

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 21-200

CORRESPONDENCE



DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-200

Food and Drug Administration
Rockville MD 20857

Novartis Pharmaceuticals Corporation
Attention: Donna Vivello
Associate Director Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Vivello:

Please refer to your pending new drug application (NDA) dated February 11, 2000, received February 11, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zelmac™ (tegaserod hydrogen maleate) Tablets.

We request that you commit in writing to conducting the following studies post approval:

1. A long-term (1 year) maintenance study conducted in the U.S. in women with constipation-predominant IBS.
2. ~~_____~~
3. An epidemiological study of a sufficient number of women on the recommended regimen of Zelmac™, 6 mg b.i.d., to address the lingering concerns about laparotomies, ovarian cysts, and appendicitis

If you have any questions, call Paul E. Levine, Jr., R.Ph., Regulatory Project Manager, at (301) 827-7310.

Sincerely,

/S/

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM

DATE: July 10, 2002

FROM: Paul E. Levine, Jr., R.Ph.; Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Labeling Comments
NDA 21-200; Zelnorm™ (tegaserod maleate) Tablets

TO: Donna Vivelo, Associate Director, Drug Regulatory Affairs

Please refer to your February 28, 2002, resubmission in response to our August 15, 2001, Not Approvable letter for Zelnorm™ (tegaserod maleate) Tablets.

We further refer to your July 09, 2002, submission containing proposed labeling revisions for Zelnorm.

We are reviewing your revised labeling and have the following recommendations concerning the proposed patient package insert.

1. Revise the format of the patient package insert to be consistent with the format required for Medications Guides under 21 CFR §208.20
2. Change lines 6-8 under the section, INFORMATION FOR THE PATIENT:

From:

[]

To:

"Read this information carefully before you start taking ZELNORM (ZEL-norm). Read the information you get each time you get more ZELNORM. There may be new information. This information does not take the place of talking to your doctor about your medical condition or treatment."

3. Delete the section, _____
4. Change lines 20-22 under the section, WHAT IS ZELNORM?:

From:

[]

To:

[]

5. Change lines 23-32 under the section, WHAT IS ZELNORM?:

From:

[

]

To:

"Zelnorm increases the movement of stools (bowel movement) through the bowels. Zelnorm does not cure IBS. For those who are helped, Zelnorm reduces pain and discomfort in the abdominal area (stomach area), bloating, and constipation. If you stop taking Zelnorm, your IBS symptoms may return within 1 or 2 weeks."

6. Under the section, WHAT ARE THE POSSIBLE SIDE EFFECTS OF ZELNORM?, delete lines 68:

NDA 21-200
Memorandum: 07/10/02
Page 3

Also, include the risk of abdominal surgery in this section.

We request that you resubmit your revised patient package insert with the changes recommended above, as soon as possible.

If you have any questions, you may contact me at (301) 446-8347.

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/s/

Paul Levine
7/10/02 03:59:17 PM
CSO

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NDA 21-200 / SE -

RPM Paul E. Levine, Jr. Phone 301-443-8347

☐ 505(b)(2) Reference listed drugReview priority: ☐ S ☒ P

Pivotal IND(s)	IND
1	1
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100	100

Primary September 01, 2002

Other (e.g., orphan, OTC)

Secondary

Indicate N/A (not applicable), X (completed), or add a comment.

◆ **User Fee Information:** ☒ **User Fee Paid**
☐ **User Fee Waiver** (attach waiver notification letter)
☐ **User Fee Exemption**

◆ Action Letter..... ☒ AP ☐ AE ☐ NA

FDA revised labeling and reviews.....

See July 03 ,10, and 16, 2002
meeting minutes

Original proposed labeling (package insert, patient package insert)

$$\frac{c}{x}$$

Other labeling in class (most recent 3) or class labeling.....

X

Has DDMAC reviewed the labeling? ☒ Yes

☒ Yes (include review) ☐ No

Immediate container and carton labels

X

Nomenclature review

X

◆ **Application Integrity Policy (AIP)** ☐ Applicant is on the AIP. This application ☐ is ☒ **is not** on the AIP

Exception for review (Center Director's memo).....

NA

OC Clearance for approval.....

NA

Continued \Rightarrow

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-200 /SE -

Drug tegaserod hydrogen maleate Applicant Novartis Pharmaceuticals

RPM Paul E. Levine, JR. Phone 301-443-8347

☒ 505(b)(1)☐ 505(b)(2) Reference listed drug

☐Fast Track

□Rolling Review

Review priority: ☐ S ☒ P

Pivotal IND(s) IND —

Application classifications:

Chem Class 1P

Other (e.g., orphan, OTC)

PDUFA Goal Dates:

Primary June 18, 2001

Secondary

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- ◆ **User Fee Information:** ☒ User Fee Paid
☐ User Fee Waiver (attach waiver notification letter)
☐ User Fee Exemption

◆ **Action Letter**..... ☐ AP ☐ AE ☒ NA

◆ **Labeling & Labels**

FDA revised labeling and reviews.....	N/A
Original proposed labeling (package insert, patient package insert)	X
Other labeling in class (most recent 3) or class labeling.....	X
Has DDMAC reviewed the labeling?	<input type="checkbox"/> Yes (include review) <input checked="" type="checkbox"/> No
Immediate container and carton labels	X
Nomenclature review	X

◆ **Application Integrity Policy (AIP)** ☐ Applicant is on the AIP. This application ☐ is ☒ is not on the AIP.

Exception for review (Center Director's memo).....	NA
OC Clearance for approval.....	NA

Continued \Rightarrow

◆ Status of advertising (if AP action) <input type="checkbox"/> Reviewed (for Subpart H – attach review)	<input type="checkbox"/> Materials requested in AP letter
◆ Post-marketing Commitments	N/A
Agency request for Phase 4 Commitments.....	N/A
Copy of Applicant's commitments	N/A
◆ Was Press Office notified of action (for approval action only)?.....	<input type="checkbox"/> Yes <input type="checkbox"/> No
Copy of Press Release or Talk Paper.....	NA
◆ Patent	
Information [505(b)(1)]	X
Patent Certification [505(b)(2)].....	X
Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....	
◆ Exclusivity Summary	X
◆ Debarment Statement	X
◆ Financial Disclosure	
No disclosable information	See Clinical Review
Disclosable information – indicate where review is located	
◆ Correspondence/Memoranda/Faxes	X
◆ Minutes of Meetings	X
Date of EOP2 Meeting X	
Date of pre NDA Meeting X	
Date of pre-AP Safety Conference	
◆ Advisory Committee Meeting	X
Date of Meeting	June 26, 2000
Questions considered by the committee	X
Minutes or 48-hour alert or pertinent section of transcript	X
◆ Federal Register Notices, DESI documents	N/A

CLINICAL INFORMATION:

**Indicate N/A (not applicable),
X (completed), or add a
comment.**

◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo)	Pending
◆ Clinical review(s) and memoranda	X

Continued ⇨

◆ Safety Update review(s)	<u>X</u>
◆ Pediatric Information	
<input type="checkbox"/> Waiver/partial waiver (Indicate location of rationale for waiver) <input checked="" type="checkbox"/> Deferred	
Pediatric Page.....	<u>N/A</u>
<input type="checkbox"/> Pediatric Exclusivity requested? <input type="checkbox"/> Denied <input type="checkbox"/> Granted <input type="checkbox"/> Not Applicable	
◆ Statistical review(s) and memoranda	<u>X</u>
◆ Biopharmaceutical review(s) and memoranda.....	<u>X (N/A for Cycle 2)</u>
◆ Abuse Liability review(s)	<u>N/A</u>
Recommendation for scheduling	
◆ Microbiology (efficacy) review(s) and memoranda	<u>NA</u>
◆ DSI Audits	<u>X</u>
<input checked="" type="checkbox"/> Clinical studies <input type="checkbox"/> bioequivalence studies	

CMC INFORMATION:

**Indicate N/A (not applicable),
X (completed), or add a
comment.**

◆ CMC review(s) and memoranda	<u>X</u>
◆ Statistics review(s) and memoranda regarding dissolution and/or stability	<u>N/A</u>
◆ DMF review(s)	<u>X</u>
◆ Environmental Assessment review/FONSI/Categorical exemption	<u>X</u>
◆ Micro (validation of sterilization) review(s) and memoranda	<u>N/A</u>
◆ Facilities Inspection (include EES report)	
Date completed <u>June 26, 2000</u>	<input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Not Acceptable
◆ Methods Validation	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

**Indicate N/A (not applicable),
X (completed), or add a
comment.**

◆ Pharm/Tox review(s) and memoranda	<u>X</u>
◆ Memo from DSI regarding GLP inspection (if any)	<u>N/A</u>

- ◆ Statistical review(s) of carcinogenicity studies NA
- ◆ CAC/ECAC report X

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 1, 2002

TO: Victor Raczkowski, M.D. Acting Director
Division of Gastrointestinal and Coagulation Drug Products
HFD-180

VIA: Paul Levine, Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products
HFD-180

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Regulatory Health Project Manager
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Anne Trontell, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for Zelnorm™ (tegaserod maleate) Tablets, NDA 21-200

The patient labeling which follows represents the revised risk communication materials for Zelnorm™ (tegaserod maleate) Tablets. Our revisions reflect changes in format, wording, and organization that are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. Comments are bolded, italicized, and underlined.

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Draft

Labeling

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/s/

Jeanine Best
7/8/02 11:10:30 AM
CSO

Anne Trontell
7/9/02 08:17:48 AM
MEDICAL OFFICER

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Zelmac

Novartis Files New Drug Application for Zelmac(TM)(tegaserod) Tablets for the Treatment of Irritable Bowel Syndrome



EAST HANOVER, N.J., Feb. 16 /PRNewswire/ -- Novartis Pharmaceuticals Corporation today announced that it has submitted a new drug application (NDA) to the US Food and Drug Administration for Zelmac(TM) (tegaserod) tablets, an innovative treatment for the multiple symptoms of irritable bowel syndrome (IBS). A regulatory submission was also filed with the European Medicines Evaluation Agency (EMEA).

Phase III studies have demonstrated that within the first week after starting treatment, Zelmac therapy provided statistically significant relief of IBS symptoms in patients who suffered primarily from abdominal pain and constipation.

"Zelmac offers an entirely new approach to treat the multiple symptoms of irritable bowel syndrome, a debilitating disorder of GI function that involves altered motility and an increase in pain perception," said Marvin M. Schuster, M.D., Professor of Medicine, Johns Hopkins University of Medicine, Baltimore, Md. "Lack of satisfactory therapies for IBS has been frustrating for both physicians and patients. Zelmac could provide a valuable new option since it improves motility and may reduce pain perception."

IBS is one of the most common disorders of function of the gastrointestinal (GI) tract, affecting up to 20 percent of the Western population. It is a chronic condition characterized by abdominal pain, bloating, and symptoms associated with irregular bowel function, such as constipation, diarrhea or an alternating pattern between the two. IBS is the second most common cause of work-related absenteeism in the US. It accounts for one in four GI visits and costs the US healthcare system \$8 billion annually. To date, no medication has proven to be safe and effective in treating IBS patients who suffer from abdominal pain, constipation and bloating as their primary symptoms.

"While all IBS sufferers experience pain, it is important to understand that the majority of patients also have constipation as a primary symptom," said Dr. Schuster. "The prevalence of constipation makes the potential availability of Zelmac attractive for treating the multiple symptoms of IBS patients."

Study Results

The filing submitted to the regulatory authorities includes data from three phase III clinical studies of Zelmac, involving more than 2,500 patients in 15 countries.

Two multicenter, double-blind, placebo-controlled studies of similar design involving 1,680 patients found those treated with Zelmac showed clinically relevant and statistically significant relief of symptoms as measured by the Subject's Global Assessment (SGA) of relief. SGA of relief is a global assessment that incorporates symptoms of abdominal pain, overall well being and altered bowel function. Significant improvement of symptoms was demonstrated within the first week and was sustained over the course of the 12-week treatment period.

Specific effects of Zelmac on IBS symptoms were also assessed through analysis of a daily diary kept by the patients. Zelmac was found to significantly reduce abdominal pain in both studies and bloating in one study. Additionally, Zelmac increased the number of bowel movements per day and reduced the number of days with no bowel movements. Zelmac also improved bowel function as early as day one.

Safety and Tolerability

Zelmac was found to be well tolerated with side effects comparable to placebo. Diarrhea was the predominant adverse event reported more often in the treatment groups (12% on Zelmac vs. 5% on placebo). In most cases, the diarrhea occurred early, was transient, and resolved with continued therapy. Only 1.6% of patients discontinued Zelmac therapy due to diarrhea. A long-term study of IBS patients treated up to 12 months, reported a similar safety and tolerability profile.

About Zelmac

ONSET ACTION
EFFICACY
INDICATION

"multiple symptoms"

EFFICACY

predominant

QOL

Label says to A/C
IF DIARRHEA

target and act on 5-HT4 receptors present throughout the GI tract. These serotonin receptors are believed to play a key role in pain perception and GI motility. By acting on the 5-HT4 receptor pathway, Zelmac reduces abdominal pain and may normalize altered GI function in IBS patients who suffer from abdominal pain, constipation and bloating as their predominant symptoms.

Other Potential Indications

Novartis is currently conducting clinical trials studying Zelmac as a potential treatment for gastroesophageal reflux disease (GERD).

"Zelmac is designed to tackle one of the most common digestive tract disorders," said A. N. Karabelas, CEO Novartis Pharma AG. "It may offer significant benefits to IBS patients and could help address one of the leading causes of lost days from work. The filing also represents an important milestone for Novartis as it enters the gastrointestinal therapeutic market."

Novartis

Novartis Pharmaceuticals Corporation researches, develops, manufactures and markets leading innovative prescription drugs used to treat a number of diseases and conditions, including central nervous system disorders, organ transplantation, cardiovascular diseases, dermatological diseases, respiratory disorders, cancer and arthritis. The company's mission is to improve people's lives by pioneering novel healthcare solutions.

Located in East Hanover, Novartis Pharmaceuticals Corporation is an affiliate of the Novartis Group, a world leader in healthcare with core businesses in pharmaceuticals, consumer health, generics, eye-care, and animal health. In 1998, the Group (including Agribusiness) achieved sales of USD 21.8 billion and invested more than USD 2.6 billion in R&D. Headquartered in Basel, Switzerland, Novartis employs about 82,000 people and operates in over 140 countries around the world. The Group recently announced plans to spin off its Crop Protection and Seeds sectors and to merge them with the agrochemicals business of AstraZeneca in the second half of 2000.

CONTACT: Media - Geoffrey Cook of Novartis Pharmaceuticals Corporation, 908-781-5486; Jennifer Bryda of Ruder Finn, 212-593-6426; or Investor - Joe Shepers of Novartis Corporation, 908-522-6899.

Novartis Pharmaceuticals Corporation

Company News On Call:

<http://www.prnewswire.com/comp/164550.html> or fax, 800-758-5804, ext. 164550

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NDA 21-200

INFORMATION REQUEST LETTER

Novartis Pharmaceuticals Corporation
Attention: Donna Vivelo
Associate Director Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Vivelo:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zelnorm™ (tegaserod) Tablets.

We also refer to the resubmission to your new drug application, dated February 28, 2002.

We are reviewing your submission and request that you provide the primary efficacy analysis, applied to the first rather than to the third month of treatment, for the three clinical trials. This analysis should include data on the number of patients who were either (a) completely or considerably relieved for at least two of the first four weeks or (b) at least somewhat relieved for all the first four weeks.

In addition, please find attached our comments to your proposed labeling submitted on February 28, 2002.

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call Paul E. Levine, Jr., R.Ph., Regulatory Health Project Manager, at 301-827-7310.

Sincerely,

{See appended electronic signature page}

Victor F. Raczkowski, M.D., M.Sc.
Acting Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Joyce Korvick
6/18/02 02:01:05 PM
for Victor Raczkowski

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Labeling Attachment:

(See, *June 19, 2002, Telecon Minutes*)

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WITHHOLD 45 PAGE (S)

Draft

Labeling

Office of Drug Safety

Memo

To: Victor Raczkowski, M.D.
Acting Director, Division of Gastro-Intestinal and Coagulation Drug Products
HFD-180

From: Alina R. Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

Through: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

CC: Paul E. Levine, Jr., R.Ph.
Project Manager
HFD-180

Date: June 27, 2002

Re: ODS Consult 01-0056-1; Zelnorm (Tegaserod Hydrogen Maleate Tablets)
2 mg and 6 mg; NDA 21-200.

This memorandum is in response to a June 17, 2002 request from your Division for a re-review of the proprietary name, Zelnorm.

DMETS has not identified any additional proprietary or established names that have the potential for confusion with Zelnorm since we conducted our initial review on April 4, 2001 (OPDRA consult 01-

0056) that would render the name objectionable. Therefore, we have no objections to the use of this proprietary name.

DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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/s/

Alina Mahmud
6/27/02 09:12:32 AM
PHARMACIST

Carol Holquist
6/27/02 10:56:26 AM
PHARMACIST

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U.S. Food and Drug Administration

FDA Talk Paper

FDA Talk Papers are prepared by the Press Office to guide FDA personnel in responding with consistency and accuracy to questions from the public on subjects of current interest. Talk Papers are subject to change as more information becomes available.

T02-33
July 24, 2002

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA APPROVES FIRST TREATMENT FOR WOMEN WITH CONSTIPATION-PREDOMINANT IRRITABLE BOWEL SYNDROME

The Food and Drug Administration (FDA) today announced the approval of Zelnorm tablets (tegaserod maleate). This drug is the first to receive FDA-approval for short-term treatment of women with irritable bowel syndrome (IBS) whose primary bowel symptom is constipation. The safety and effectiveness of Zelnorm in men have not been established.

Zelnorm increases the movement of stools (fecal matter) through the bowels. Zelnorm does not cure IBS, nor does it treat diarrhea-predominant IBS. Zelnorm reduces pain and discomfort in the abdominal area, and reduces bloating and constipation.

FDA based its decision to approve Zelnorm on the results of three randomized, double-blind, placebo-controlled clinical studies each lasting 12 weeks.

During the studies, patients were asked each week to rate their overall well-being, symptoms of abdominal discomfort and pain, and altered bowel habits.

At the end of the third month of the studies, the proportion of patients responding favorably to Zelnorm was greater than the proportion of patients responding to placebo. The differences in response rates for Zelnorm vs. placebo were greater at month 1 than month 3 suggesting efficacy may decrease over time. The efficacy of Zelnorm beyond 12 weeks has not been studied.

The adverse event reported most often in association with Zelnorm compared to placebo was diarrhea (9% of patients receiving Zelnorm compared to 4% of patients receiving placebo). The majority of the patients treated with Zelnorm who reported diarrhea had a single episode. In most cases, diarrhea occurred within the first week of treatment. Typically, diarrhea resolved without patients having to discontinue Zelnorm therapy. The discontinuation rate from the studies due to diarrhea was 1.6%.

In addition, an increase in abdominal surgeries was observed in patients on Zelnorm (0.3%) compared to placebo (0.2%) in the clinical studies. The increase was primarily due to gall bladder removals reported in patients treated with Zelnorm (0.17%) compared to placebo (0.06%). A causal relationship between abdominal surgeries and Zelnorm has not been established.

Today's action follows the recommendation for approval made by FDA's Gastrointestinal Drugs Advisory Committee on June 26, 2000. FDA had required additional efficacy and safety information following that meeting because there were conflicting results in the efficacy studies and outstanding safety questions.

Novartis Pharmaceuticals Corporation of East Hanover, N.J., is the sponsor of the approved New Drug Application (NDA) for Zelnorm.

###

[Media Contacts](#) | [FDA News Page](#) | [FDA Home Page](#)

Office of Public Affairs
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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		ODS POSTMARKETING SAFETY REVIEW	
TO: Victor Raczowski, M.D., Acting Director Division of Gastrointestinal and Anticoagulant Drug Products HFD-180		FROM: Ann Corken Mackey, RPh, MPH Safety Evaluator Division of Drug Risk Evaluation (DDRE) HFD-430	
		ODS PID # D020270 Date: June 6, 2002	
DATE REQUESTED:		REQUESTOR/Phone #:	
DATE RECEIVED:			
DRUG (Est): Tegaserod		NDA/IND # 21-200	SPONSOR: Novartis
DRUG NAME (Trade): Zelnorm		THERAPEUTIC CLASSIFICATION:	
EVENT: All events			
<p>Executive Summary: The sponsor for tegaserod, Novartis, is seeking approval for their drug in the United States. The review division for tegaserod (HFD-180) has concerns about biliary tree events (i.e., one case of sphincter of Oddi spasm, one case of bile duct stone, one case of cholestatic hepatocellular effects) as identified from the spontaneous reporting system. (1) Tegaserod has been approved for marketing in 18 countries and has been launched in 4 countries. (1) Note that the specified cases were not reported through AERS. The medical officer team leader in HFD-180 requested a search of the Adverse Event Reporting System (AERS), the medical literature, and the World Health Organization (WHO) for postmarketing reports for tegaserod because of reports of biliary tree events received from the Sponsor. The following information is provided:</p> <ol style="list-style-type: none"> 1. AERS: A search of AERS identified one report for tegaserod submitted in May, 2001. The reporter was a consumer who had a stroke while taking tegaserod in a clinical trial. 2. Literature: A search of the medical literature found no reports of adverse events involving tegaserod. 3. WHO: A search from WHO identified no reports that specified biliary tree events; however, adverse events such as abdominal pain, nausea, etc. could be associated with these events. The printout from WHO is attached (note that _____ and _____). 			
Relevant Product Labeling: N/A			
Search Date: June 18, 2002		Search Type(s): AERS Literature WHO	
Search Criteria: Drug Names: Tegaserod (Zelnorm) MEDDRA Terms: All events			
Search Results: <ol style="list-style-type: none"> 1. AERS: A search of AERS identified one report for tegaserod submitted in May, 2001. The reporter was a consumer who had a stroke while taking tegaserod in a clinical trial. 2. Literature: A search of the medical literature found no reports of adverse events involving tegaserod. 3. WHO: A search from WHO identified no reports that specified biliary tree events; however, adverse events such as abdominal pain, nausea, etc. could be associated with these events. The printout from WHO is attached (note that _____ and _____). 			
Reference: <ol style="list-style-type: none"> 1. Gallo-Torres H. Medical Officer's Review of Safety Update for Zelnorm. NDA 21-200. FDA DFS System, June 17, 2002. 			
Discussion / Conclusions: At HFD-180's request, the following information is provided, including search results from AERS, search results from the medical literature, and a printout from WHO.			
Reviewer's Signature / Date: Ann Corken Mackey 6/19/02		Team Leader's Signature / Date: Lanh Green 6/19/02	
Division Director Signature / Date: Julie Beitz 6/19/02			

Cc: NDA # 21-200

HFD-430 Beitz/Green/Mackey/Guinn/Birdsong/Drug

HFD-180 Raczkowski/Korvick/Gallo-Torres/Project Manager

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ATTACHMENT

Adverse reactions to drugs

Date: 2002-06-18

Search covers total holding

TEGASEROD

Body as a whole - general disor	
ALLERGY	1
CHEST PAIN	1
FATIGUE	2
FEVER	1
PAIN	2
Centr & periph nervous system d	
COMA	1
DIZZINESS	3
HEADACHE	1
Gastro-intestinal system disord	
ABDOMINAL PAIN	3
DIARRHOEA	7
GASTRITIS	1
NAUSEA	3
TENESMUS	1
VOMITING	1
Heart rate and rhythm disorders	
ARRHYTHMIA	1
TACHYCARDIA	2
Metabolic and nutritional disor	
HYPOGLYCAEMIA	1
Respiratory system disorders	
DYSPOEA	2
Skin and appendages disorders	
SWEATING INCREASED	1
Urinary system disorders	
POLYURIA	1
Vascular (extracardiac) disorde	
PERIPHERAL ISCHAEMIA	1
Vision disorders	
DIPLOPIA	3
STRABISMUS	3

APPEARS THIS WAY
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Adverse reactions to drugs

Date: 2002-06-18

Search covers total holding

Summary on investigated terms

TEGASEROD

ABDOMINAL PAIN	3
ALLERGY	1
ARRHYTHMIA	1
CHEST PAIN	1
COMA	1
DIARRHOEA	7
DIPLOPIA	3
DIZZINESS	3
DYSPNOEA	2
FATIGUE	2
FEVER	1
GASTRITIS	1
HEADACHE	1
HYPOGLYCAEMIA	1
NAUSEA	3
PAIN	2
PERIPHERAL ISCHAEMIA	1
POLYURIA	1
STRABISMUS	3
SWEATING INCREASED	1
TACHYCARDIA	2
TENESMUS	1
VOMITING	1

43

APPEARS THIS WAY
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Search performed on:

Year(s): All

Countries: All

Drug(s): TEGASEROD

Reaction(s): All

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ann Corken
6/19/02 03:42:30 PM
PHARMACIST

Julie Beitz
6/25/02 10:41:35 AM
DIRECTOR

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consult rev. *Levine*
21-2-00

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
 PUBLIC HEALTH SERVICE
 FOOD AND DRUG ADMINISTRATION
 CENTER FOR DRUG EVALUATION AND RESEARCH

PID# D000468

DATE: **MAY 30 2000**

FROM: Toni Piazza-Hepp, Pharm.D., Team Leader
 Division of Drug Risk Evaluation II (DDREII)

THROUGH: Evelyn M. Rodriguez, M.D., M.P.H. *05/30/00*
 DDREII/HFD-440

TO: Lilia Talarico, M.D., Director
 Division of Gastrointestinal and Coagulation Drug Products
 HFD-180

SUBJECT: OPDRA POSTMARKETING SAFETY REVIEW:
 Drug-Associated Ovarian Cancer

Executive Summary:

A consult was received from HFD-180 on 4/4/2000 requesting information about drugs that cause or have been associated with the incidence of ovarian cancer, which was stimulated by the finding of ovarian cysts in clinical studies for the drug tegaserod (Zelmac), an NDA under current review in HFD-180. The on-line PDR, the Adverse Event Reporting System (AERS) and the literature were searched. Information regarding drug-associated ovarian cancer indicate that agents which stimulate ovulation (fertility drugs) may increase the risk, while agents which decrease ovulation (oral contraceptives) appear to decrease the risk. The literature also describes hormone replacement therapy, talcum powder and tamoxifen as other agents which may be associated with an increased risk of ovarian cancer, but these findings appear to be controversial.

Background:

A consult was received from HFD-180 on 4/4/2000 requesting information about drugs that cause or have been associated with the incidence of ovarian cancer. This request was stimulated by the finding of ovarian cysts in clinical studies for the Novartis drug tegaserod (Zelmac), an NDA under current review in HFD-180 for the treatment of irritable bowel syndrome.

Methods and Results:

To approach this broad request, three methods were used. First was a search of the on-line Physician's Desk Reference for any mention of "ovarian cancer" in labeling. The second was a search of the Adverse Event Reporting System (AERS) under all drug products and the MedDRA High Level Term Ovarian cancer (exc germ cell and sarcoma). The results of the first two methods are presented on pages 2 and 3. Finally, a Medline search was performed as described on page 3.

“Ovarian cancer” included in labeling where not an indication for use

(Source: PDR Electronic library. Search date 4/20/2000)

CLOMID (clomiphene citrate)

WARNINGS

A causal relationship between ovarian hyperstimulation and ovarian cancer has not been determined. However, because a correlation between ovarian cancer and nulliparity, infertility, and age has been suggested, if ovarian cysts do not regress spontaneously, a thorough evaluation should be performed to rule out the presence of ovarian neoplasia.

PRECAUTIONS

Ovarian Cancer

Prolonged use of clomiphene citrate tablets USP may increase the risk of a borderline or invasive ovarian tumor (see ADVERSE REACTIONS).

ADVERSE REACTIONS

Ovarian cancer has been infrequently reported in patients who have received fertility drugs. Infertility is a primary risk factor for ovarian cancer ; however, epidemiology data suggest that prolonged use of clomiphene may increase the risk of a borderline or invasive ovarian tumor.

SEROPHENE (clomiphene citrate)

PRECAUTIONS

Ovarian cancer has been reported in a very small number of infertile women who have been treated with clomiphene citrate. A causal relationship between treatment with clomiphene citrate and ovarian cancer has not been established.

Oral Contraceptive class labeling:

NONCONTRACEPTIVE HEALTH BENEFITS

The following noncontraceptive health benefits related to the use of oral contraceptives are supported by epidemiological studies which largely utilized oral-contraceptive formulations containing doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg of mestranol.

Effects on menses:

Increased menstrual cycle regularity.

Decreased blood loss and decreased incidence of iron-deficiency anemia.

Decreased incidence of dysmenorrhea.

Effects related to inhibition of ovulation:

Decreased incidence of functional ovarian cysts.

Decreased incidence of ectopic pregnancies.

Effects from long-term use:

Decreased incidence of fibroadenomas and fibrocystic disease of the breast.

Decreased incidence of acute pelvic inflammatory disease.

Decreased incidence of endometrial cancer.

Decreased incidence of ovarian cancer .

Ovarian cancer identified as an adverse event term in AERS

There were 262 reports in AERS where a term for ovarian cancer was coded as an adverse event. These 262 reports were received by the FDA beginning in 1994; this indicates that 1994 was the first year a specific adverse event term for ovarian cancer was created in the COSTART dictionary¹. Attachment #1 provides a list of drugs with two or more reports of ovarian cancer. The drugs with five or more reports for ovarian cancer are listed below; for this listing report numbers have been combined for active ingredients that may exist as more than one salt or more than one marketed product. Please note that these are raw numbers and some of the reports may represent duplicates.

Drugs with five or more reports of ovarian cancer

Paclitaxel	42
Tamoxifen citrate	22
Clomiphene citrate	21
Methotrexate or Methotrexate sodium	19
Clozapine	11
Gonadotropin Human menopausal	7
Estrogens, conjugated	7
Levonorgestrel (Norplant)	5

Literature Findings:

The Medline Thesaurus term "ovarian neoplasms" and the MeSH term "chemically induced" (limited to English language, human data, and the years 1990-2000) were utilized to attempt to focus on possible discussions or cases of drug associated ovarian cancer. This search strategy yielded 113 articles. A listing of those articles is attached for your review.

DISCUSSION:

According to the Merck Manual (on-line; 1999) and Harrison's Principles of Internal Medicine (on-line; 1999), ovarian cancer is the second most commonly diagnosed gynecologic malignancy and the fourth leading cause of cancer-related deaths in women in the US, affecting predominantly perimenopausal and postmenopausal women. In 1996 there were 26,700 new cases diagnosed and 14,800 deaths. About 1 in 70 women eventually develops ovarian cancer and 1 in 100 women dies of it. Risk factors include nulliparity, infertility and family history. Each pregnancy reduces the ovarian cancer risk by about 10 percent. Repeated ovulation ("incessant ovulation") may provide

¹ COSTART was in use in between 1969 and October 1997; MedDRA replaced COSTART in November 1997.


opportunity for somatic gene deletions and mutations to occur, which can contribute to tumor initiation and progression.

The literature addresses ovulatory stimulants used in infertility, hormone replacement therapy and talcum powder as agents with possible links to an increased risk of ovarian cancer, however, these associations are often controversial. The clomiphene labeling contains information regarding a possible association between its use and ovarian cancer. Information was also found in the literature regarding a decreased risk of ovarian cancer in relation to oral contraceptive use; these data are reflected in the current oral contraceptive labeling. These findings are considered consistent with the "incessant ovulation" theory. Additionally, a single study of OTC analgesic use was identified (record 31) which reported a decreased risk of ovarian cancer.

Regarding drugs identified in the AERS search, paclitaxel, methotrexate and tamoxifen are agents that have been utilized in the treatment of ovarian cancer. Thus, these reports may represent failure of effect in treating ovarian cancer, progression of ovarian cancer, or if ovarian cancer was indeed reported as the adverse event. Tamoxifen was suspected as the cause of ovarian cancer in a published case report (record 34). Clomiphene and gonadotropin are ovulatory stimulants, which (as stated previously) are generally considered to increase risk. An unexpected finding was clozapine with 11 reports in AERS. This may simply be reflective of the fact that there are over 18,000 cases of any nature in AERS with clozapine. An alternative interesting explanation may be that schizophrenic patients once given treatment will begin to voice symptoms that may lead to detection of previously undiagnosed cancer² or perhaps that schizophrenics may have a higher rate of infertility than nonschizophrenics.

CONCLUSION:

Information regarding drug-associated ovarian cancer indicate that agents which stimulate ovulation (fertility drugs) may increase the risk, while agents which decrease ovulation (oral contraceptives) appear to decrease the risk. The literature also describes hormone replacement therapy, talc and tamoxifen as other agents which may be associated with an increased risk of ovarian cancer, but these findings appear to be controversial.


Toni Piazza-Hepp, Pharm.D.

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² Avnon-M and Stolerman-I, Clozapine, Cancer and Schizophrenia, Am J Psychiatry 1993; 150:1562-3.

cc:

HFD-180

NDA 21-200

Project manager / Div Director / Medical Officer/Medical Team Leader /
Division files

HFD-440

Rodriguez/ Piazza-Hepp/Corken/Chron/Drug

HFD-400

Honig

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Statistical Summary Report

Cases By Suspect And Other Product

Role	Active Ingredient	Product	Count Of Cases	Death	% Death	Serious	% Serious	Non Serious
S	Paclitaxel	Taxol	42	40	95.24	42	100.00	0
	Tamoxifen Citrate	Nolvadex	22	6	27.27	16	72.73	4
	Clomiphene Citrate	Clomid	16	1	6.25	14	87.50	0
	Methotrexate	Methotrexate	12	0	0.00	12	100.00	0
	Gonadotropin Human Menopausal	Gonadotropin Human Menopausal	7	0	0.00	7	100.00	0
	Methotrexate Sodium	Methotrexate	6	0	0.00	6	100.00	0
	Clozapine	Clozaril (Clozapine)	5	3	60.00	5	100.00	0
	Levonorgestrel	Norplant System	5	0	0.00	5	100.00	0
	Tamoxifen Citrate	Tamoxifen	5	0	0.00	1	20.00	0
	Estrogens, Conjugated	Premarin	5	1	20.00	5	100.00	0
	Gemcitabine Hydrochloride	Gemcitabine Hydrochloride	4	4	100.00	4	100.00	0
	Topotecan	Topotecan	4	3	75.00	4	100.00	0
	Amlodipine Besylate	Norvasc Tablets	4	1	25.00	4	100.00	0
	Gemcitabine Hydrochloride	Gemzar (Gemcitabine Hydrochloride)	4	4	100.00	4	100.00	0
	Interferon Beta-1a	—	3	0	0.00	3	100.00	0
	Clozapine	Clozaril	3	0	0.00	3	100.00	0
	Carboplatin	—	3	3	100.00	3	100.00	0
	Levonorgestrel	Norplant	3	0	0.00	3	100.00	0
	Gonadotropin Chorionic Human	Gonadotropin, Chorionic, Human	3	0	0.00	2	66.67	0
	Gemcitabine Hydrochloride	Gemzar	3	3	100.00	3	100.00	0
	Raloxifene Hydrochloride	Evista	3	0	0.00	3	100.00	0
	Medroxyprogesterone Acetate	Depo-Provera	3	0	0.00	2	66.67	0
	Cisplatin	—	2	1	50.00	2	100.00	0
	Glatiramer Acetate	Copaxone	2	0	0.00	2	100.00	0
	Tacrine Hydrochloride	Cognex	2	0	0.00	2	100.00	0
	Warfarin Sodium	Coumadin	2	0	0.00	2	100.00	0
	Estrogens, Conjugated	Premarin Tablet	2	0	0.00	2	100.00	0

Attachment #1

04/20/2000

FDA Adverse Event Reporting System (AERS)

Statistical Summary Report Cases By Suspect And Other Product

Role	Active Ingredient	Product	Count Of Cases	Death	% Death	Serious	% Serious	Non Serious
S	Menotropins (Fsh;Lh)	Pergonal	2	1	50.00	1	50.00	0
	Luteinizing Hormone	Pergonal	2	1	50.00	1	50.00	0
	Carboplatin	Paraplatin	2	0	0.00	2	100.00	0
	Nafarelin Acetate	—	2	0	0.00	2	100.00	0
	Atorvastatin Calcium	Lipitor (Atorvastatin)	2	0	0.00	2	100.00	0
	Clozapine	—	2	0	0.00	2	100.00	0
	Topotecan Hydrochloride	Hycamtin	2	1	50.00	2	100.00	0
	Goserelin Acetate	Zoladex	2	0	0.00	2	100.00	0
	Paclitaxel	Taxol Inj	2	0	0.00	2	100.00	0
	Dexfenfluramine Hydrochloride	Redux	2	0	0.00	2	100.00	0
	Medroxyprogesterone Acetate	Provera	2	0	0.00	2	100.00	0
	Encainide Hydrochloride	Enkaid	2	2	100.00	2	100.00	0
	Epoetin Alfa	—	2	2	100.00	2	100.00	0
	Etidronate Disodium	Didronel	2	0	0.00	1	50.00	0
	Warfarin Sodium	Coumadin (Crystalline Warfarin Sodium)	2	0	0.00	2	100.00	0

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Attachment #2

Usage is subject to the terms and conditions of the subscription and License Agreement and the applicable Copyright and intellectual property protection as dictated by the appropriate laws of your country and/or International Convention.

No.	Records	Request
1	410	explode "Ovarian-Neoplasms"/ chemically-induced
2	7788489	english in la
3	6764047	human in tg
4	179	(english in la) and (human in tg) and #1
5	3970789	PY = 1990-2000
* 6	113	#4 and (PY = 1990-2000)

Record 1 of 113 - MEDLINE EXPRESS (R) 2000/01-2000/05

TI: Use of HRT and the subsequent risk of cancer.

AU: Beral-V; Banks-E; Reeves-G; Appleby-P

SO: J-Epidemiol-Biostat. 1999; 4(3): 191-210; discussion 210-5

ISSN: 1359-5229

LA: ENGLISH

AN: 20158506

Record 2 of 113 - MEDLINE EXPRESS (R) 2000/01-2000/05

TI: Ovarian cancer and ovulation induction drugs--is there a link?

AU: Koscec-V; Bukovic-D; Grubisic-G; Fures-R

SO: Coll-Antropol. 1999 Dec; 23(2): 633-9

ISSN: 0350-6134

LA: ENGLISH

AN: 20111717

Record 3 of 113 - MEDLINE EXPRESS (R) 2000/01-2000/05

TI: HRT and cancer risk: separating fact from fiction.

AU: Schneider-HP

SO: Maturitas. 1999 Nov; 33 Suppl 1: S65-72

ISSN: 0378-5122

LA: ENGLISH

AN: 20125259

Record 4 of 113 - MEDLINE EXPRESS (R) 2000/01-2000/05

TI: Luteinizing hormone induction of ovarian tumors: oligogenic differences between mouse strains dictates tumor disposition.

AU: Keri-RA; Lozada-KL; Abdul-Karim-FW; Nadeau-JH; Nilson-JH

SO: Proc-Natl-Acad-Sci-U-S-A. 2000 Jan 4; 97(1): 383-7

ISSN: 0027-8424

LA: ENGLISH

AN: 20087258

Record 5 of 113 - MEDLINE EXPRESS (R) 2000/01-2000/05

TI: Infertility and ovarian cancer [news]

AU: Chatterjee-SK

SO: J-Indian-Med-Assoc. 1999 Feb; 97(2): 69

ISSN: 0019-5847

LA: ENGLISH

AN: 20016916

Record 6 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Risk of cancer after use of fertility drugs with in-vitro fertilisation [see comments]

AU: Venn-A; Watson-L; Bruinsma-F; Giles-G; Healy-D

SO: Lancet. 1999 Nov 6; 354(9190): 1586-90

ISSN: 0140-6736

LA: ENGLISH

AN: 20023328

Record 7 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Complexity of surveillance for cancer risk associated with in-vitro fertilisation [comment]

AU: Rossing-MA; Daling-JR

SO: Lancet. 1999 Nov 6; 354(9190): 1573-4

ISSN: 0140-6736

LA: ENGLISH

AN: 20023322

Record 8 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Risks of hormone replacement therapy [letter]

AU: Grant-EC; Price-EH; Steel-CM

SO: Lancet. 1999 Oct 9; 354(9186): 1302-3

ISSN: 0140-6736

LA: ENGLISH

AN: 99448974

Record 9 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Hormone replacement therapy and risk of epithelial ovarian cancer.

AU: Purdie-DM; Bain-CJ; Siskind-V; Russell-P; Hacker-NF; Ward-BG; Quinn-MA; Green-AC

SO: Br-J-Cancer. 1999 Oct; 81(3): 559-63

ISSN: 0007-0920

LA: ENGLISH

AN: 99435643

Record 10 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Correlation of asbestos fiber burdens in fallopian tubes and ovarian tissue.

AU: Heller-DS; Gordon-RE; Katz-N

SO: Am-J-Obstet-Gynecol. 1999 Aug; 181(2): 346-7

ISSN: 0002-9378

LA: ENGLISH

AN: 99383843

Record 11 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Induction of ovulation and borderline ovarian cancer--the hormonal connection?

AU: Shushan-A; Paltiel-O; Schenker-JG

SO: Eur-J-Obstet-Gynecol-Reprod-Biol. 1999 Jul; 85(1): 71-4

ISSN: 0301-2115

LA: ENGLISH

AN: 99355279

Record 12 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Papillary serous carcinoma of the ovary following prolonged tamoxifen treatment.

AU: Seoud-M; Salem-Z; Shamseddine-A; Khabbaz-A; Zaatari-G; Khalil-A

SO: Eur-J-Gynaecol-Oncol. 1999; 20(3): 237-9

ISSN: 0392-2936

LA: ENGLISH

AN: 99336679

Record 13 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study [letter; comment]

AU: Cramer-DW

SO: Obstet-Gynecol. 1999 Jul; 94(1): 160-1

ISSN: 0029-7844

LA: ENGLISH

AN: 99316605

Record 14 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Re: Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone [letter; comment]

AU: Hamilton-TC

SO: J-Natl-Cancer-Inst. 1999 Apr 7; 91(7): 650-1

ISSN: 0027-8874

LA: ENGLISH

AN: 99217954

Record 15 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Lactose absorption in patients with ovarian cancer.

AU: Meloni-GF; Colombo-C; La-Vecchia-C; Ruggiu-G; Mannazzu-MC; Ambrosini-G; Cherchi-PL

SO: Am-J-Epidemiol. 1999 Jul 15; 150(2): 183-6

ISSN: 0002-9262

LA: ENGLISH

AN: 99339308

Record 16 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Fertility drugs and the risk of breast and ovarian cancers: results of a long-term follow-up study.

AU: Potashnik-G; Lerner-Geva-L; Genkin-L; Chetrit-A; Lunenfeld-E; Porath-A

SO: Fertil-Steril. 1999 May; 71(5): 853-9

ISSN: 0015-0282

LA: ENGLISH

AN: 99246076

Record 17 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Genital talc exposure and risk of ovarian cancer.

AU: Cramer-DW; Liberman-RF; Titus-Ernstoff-L; Welch-WR; Greenberg-ER; Baron-JA; Harlow-BL

SO: Int-J-Cancer. 1999 May 5; 81(3): 351-6

ISSN: 0020-7136

LA: ENGLISH

AN: 99224654

Record 18 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study [see comments]

AU: Wong-C; Hempling-RE; Piver-MS; Natarajan-N; Mettlin-CJ

SO: Obstet-Gynecol. 1999 Mar; 93(3): 372-6

ISSN: 0029-7844

LA: ENGLISH

AN: 99173277

Record 19 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Hormonal therapy for menopause and ovarian cancer in a collaborative re-analysis of European studies.

AU: Negri-E; Tzonou-A; Beral-V; Lagiou-P; Trichopoulos-D; Parazzini-F; Franceschi-S; Booth-M; La-Vecchia-C

SO: Int-J-Cancer. 1999 Mar 15; 80(6): 848-51

ISSN: 0020-7136

LA: ENGLISH

AN: 99173211

Record 20 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Fertility drugs and ovarian cancer.
AU: Glud-E; Kjaer-SK; Troisi-R; Brinton-LA
SO: Epidemiol-Rev. 1998; 20(2): 237-57
ISSN: 0193-936X
LA: ENGLISH
AN: 99118085

Record 21 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: MR appearance of endometrial carcinoma and mucinous cystadenoma in a postmenopausal patient treated with tamoxifen for breast cancer.
AU: Joja-I; Asakawa-T; Ando-Y; Shiraiwa-M; Shibutani-O; Akaki-S; Kuroda-M; Mizutani-Y; Kudo-T; Hiraki-Y
SO: Radiat-Med. 1998 Jul-Aug; 16(4): 315-9
ISSN: 0288-2043
LA: ENGLISH
AN: 99029568

Record 22 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Ovarian stimulation and borderline ovarian tumors: a case-control study.
AU: Mosgaard-BJ; Lidegaard-O; Kjaer-SK; Schou-G; Andersen-AN
SO: Fertil-Steril. 1998 Dec; 70(6): 1049-55
ISSN: 0015-0282
LA: ENGLISH
AN: 99063040

Record 23 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Psychotropic medication use and risk of epithelial ovarian cancer.
AU: Harlow-BL; Cramer-DW; Baron-JA; Titus-Ernstoff-L; Greenberg-ER
SO: Cancer-Epidemiol-Biomarkers-Prev. 1998 Aug; 7(8): 697-702
ISSN: 1055-9965
LA: ENGLISH
AN: 98382348

Record 24 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Fertility drugs and malignant germ-cell tumour of ovary in pregnancy [letter]
AU: Tewari-K; Rose-GS; Balderston-KD; Porto-M; Kohler-MF
SO: Lancet. 1998 Mar 28; 351(9107): 957-8
ISSN: 0140-6736
LA: ENGLISH
AN: 98404017

Record 25 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Estrogen and progesterone receptors in benign ovarian tumors of menopausal breast cancer patients treated with tamoxifen.
AU: Cohen-I; Bernheim-J; Fishman-A; Shapira-J; Tepper-R; Beyth-Y; Cordoba-M; Yigael-D; Altaras-MM
SO: Gynecol-Obstet-Invest. 1998 Aug; 46(2): 116-22
ISSN: 0378-7346
LA: ENGLISH
AN: 98369030

Record 26 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Cancer in women with infertility.
AU: Duckitt-K; Templeton-AA
SO: Curr-Opin-Obstet-Gynecol. 1998 Jun; 10(3): 199-203
ISSN: 1040-872X
LA: ENGLISH
AN: 98283101

Record 27 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Ovarian neoplasia and subfertility treatments.
AU: Nugent-D; Salha-O; Balen-AH; Rutherford-AJ
SO: Br-J-Obstet-Gynaecol. 1998 Jun; 105(6): 584-91
ISSN: 0306-5456
LA: ENGLISH
AN: 98309362

Record 28 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Virilizing ovarian tumor of low malignant potential associated with antecedent tamoxifen use for breast cancer.
AU: Surbek-DV; Hoesli-I; Torhorst-J; Almendral-AC; Dellas-A; Holzgreve-W
SO: Gynecol-Oncol. 1998 Mar; 68(3): 293-6
ISSN: 0090-8258
LA: ENGLISH
AN: 98233503

Record 29 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Treatment for fertility and risk of ovarian tumors of borderline malignancy.
AU: Parazzini-F; Negri-E; La-Vecchia-C; Moroni-S; Polatti-A; Chiaffarino-F; Surace-M; Ricci-E
SO: Gynecol-Oncol. 1998 Mar; 68(3): 226-8
ISSN: 0090-8258
LA: ENGLISH
AN: 98233490

Record 30 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Parity, fertility drugs, and ovarian cancer [letter; comment]
AU: Vlahos-N
SO: Fertil-Steril. 1998 Jan; 69(1): 168-9

ISSN: 0015-0282

LA: ENGLISH

AN: 98117164

Record 31 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Over-the-counter analgesics and risk of ovarian cancer.

AU: Cramer-DW; Harlow-BL; Titus-Ernstoff-L; Bohlke-K; Welch-WR; Greenberg-ER

SO: Lancet. 1998 Jan 10; 351(9096): 104-7

ISSN: 0140-6736

LA: ENGLISH

AN: 98102668

Record 32 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Pesticides and cancer.

AU: Dich-J; Zahm-SH; Hanberg-A; Adami-HO

SO: Cancer-Causes-Control. 1997 May; 8(3): 420-43

ISSN: 0957-5243

LA: ENGLISH

AN: 98141151

Record 33 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Carcinogenicity studies on MTBE: critical review and interpretation.

AU: Mennear-JH

SO: Risk-Anal. 1997 Dec; 17(6): 673-81

ISSN: 0272-4332

LA: ENGLISH

AN: 98125085

Record 34 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Endometrioid adenocarcinoma of the ovary and long-term tamoxifen therapy: a coincidence or a cause for concern?

AU: Kuo-DY; Jones-J; Fields-AL; Runowicz-CD; Goldberg-GL

SO: Eur-J-Gynaecol-Oncol. 1997; 18(6): 457-60

ISSN: 0392-2936

LA: ENGLISH

AN: 98105220

Record 35 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Hormone replacement therapy and gynecological cancer.

AU: Gadducci-A; Fanucchi-A; Cosio-S; Genazzani-AR

SO: Anticancer-Res. 1997 Sep-Oct; 17(5B): 3793-8

ISSN: 0250-7005

LA: ENGLISH

AN: 98089219

Record 36 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Treatment for infertility and risk of invasive epithelial ovarian cancer.

AU: Parazzini-F; Negri-E; La-Vecchia-C; Moroni-S; Franceschi-S; Crosignani-PG

SO: Hum-Reprod. 1997 Oct; 12(10): 2159-61

ISSN: 0268-1161

LA: ENGLISH

AN: 98063866

Record 37 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Hormone replacement therapy as a risk factor for epithelial ovarian cancer: results of a case-control study [letter; comment]

AU: Weber-AM

SO: Obstet-Gynecol. 1997 Oct; 90(4 Pt 1): 641-2

ISSN: 0029-7844

LA: ENGLISH

AN: 98021342

Record 38 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Another two cases of ovarian tumours in women who had undergone multiple ovulation induction cycles.

AU: Salle-B; de-Saint-Hilaire-P; Devouassoux-M; Gaucherand-P; Rudigoz-C

SO: Hum-Reprod. 1997 Aug; 12(8): 1732-5

ISSN: 0268-1161

LA: ENGLISH

AN: 97452389

Record 39 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Estrogen replacement therapy following oophorectomy in women with a family history of ovarian cancer.

AU: Eltabbakh-GH; Piver-MS; Hempling-RE; Recio-FO; Aiduk-C

SO: Gynecol-Oncol. 1997 Jul; 66(1): 103-7

ISSN: 0090-8258

LA: ENGLISH

AN: 97378248

Record 40 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: The feasibility of assessing women's perceptions of the risks and benefits of fertility drug therapy in relation to ovarian cancer risk.

AU: Rosen-B; Irvine-J; Ritvo-P; Shapiro-H; Stewart-D; Reynolds-K; Robinson-G; Thomas-J; Neuman-J; Murphy-J

SO: Fertil-Steril. 1997 Jul; 68(1): 90-4

ISSN: 0015-0282

LA: ENGLISH

AN: 97351308

Record 41 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Fertility drugs and ovarian epithelial cancer: the endometriosis hypothesis.

AU: Paulson-RJ

SO: J-Assist-Reprod-Genet. 1997 Apr; 14(4): 228-30

ISSN: 1058-0468

LA: ENGLISH

AN: 97276319

Record 42 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Infertility, fertility drugs, and invasive ovarian cancer: a case-control study [see comments]

AU: Mosgaard-BJ; Lidegaard-O; Kjaer-SK; Schou-G; Andersen-AN

SO: Fertil-Steril. 1997 Jun; 67(6): 1005-12

ISSN: 0015-0282

LA: ENGLISH

AN: 97319533

Record 43 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Comparison of effect estimates from a meta-analysis of summary data from published studies and from a meta-analysis using individual patient data for ovarian cancer studies [see comments]

AU: Steinberg-KK; Smith-SJ; Stroup-DF; Olkin-I; Lee-NC; Williamson-GD; Thacker-SB

SO: Am-J-Epidemiol. 1997 May 15; 145(10): 917-25

ISSN: 0002-9262

LA: ENGLISH

AN: 97293769

Record 44 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Fertility drugs and ovarian cancer.

AU: Artini-PG; Fasciani-A; Cela-V; Battaglia-C; de-Micheroux-AA; D'Ambrogio-G; Genazzani-AR

SO: Gynecol-Endocrinol. 1997 Feb; 11(1): 59-68

ISSN: 0951-3590

LA: ENGLISH

AN: 97240886

Record 45 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: The impact of parity, infertility and treatment with fertility drugs on the risk of ovarian cancer. A survey.

AU: Mosgaard-BJ; Lidegaard-O; Andersen-AN

SO: Acta-Obstet-Gynecol-Scand. 1997 Feb; 76(2): 89-95

ISSN: 0001-6349

LA: ENGLISH

AN: 97201492

Record 46 of 113 - MEDLINE EXPRESS (R) 1997-1999

TI: Malignant tumors of the ovary or the breast in association with infertility: a report of thirteen cases.

AU: Unkila-Kallio-L; Leminen-A; Tiitnen-A; Lehtovirta-P; Wahlstrom-T; Ylikorkala-O

SO: Acta-Obstet-Gynecol-Scand. 1997 Feb; 76(2): 177-81

ISSN: 0001-6349

LA: ENGLISH

AN: 97201508

Record 47 of 113 - MEDLINE EXPRESS (R) 1994-1996

TI: Assessment of follicle destruction in chemical-induced ovarian toxicity.

AU: Hoyer-PB; Sipes-IG

SO: Annu-Rev-Pharmacol-Toxicol. 1996; 36: 307-31

ISSN: 0362-1642

LA: ENGLISH

AN: 96293312

Record 48 of 113 - MEDLINE EXPRESS (R) 1994-1996

TI: Ovulation induction and ovarian malignancy.

AU: Beltsos-AN; Odem-RR

SO: Semin-Reprod-Endocrinol. 1996 Nov; 14(4): 367-74

ISSN: 0734-8630

LA: ENGLISH

AN: 97142325

Record 49 of 113 - MEDLINE EXPRESS (R) 1994-1996

TI: Ovarian cancer after successful ovulation induction: a case report.

AU: Hull-ME; Kriner-M; Schneider-E; Maiman-M

SO: J-Reprod-Med. 1996 Jan; 41(1): 52-4

ISSN: 0024-7758

LA: ENGLISH

AN: 97007817

Record 50 of 113 - MEDLINE EXPRESS (R) 1994-1996

TI: Estrogen replacement therapy and risk of epithelial ovarian cancer.

AU: Risch-HA

SO: Gynecol-Oncol. 1996 Nov; 63(2): 254-7

ISSN: 0090-8258

LA: ENGLISH

AN: 97066864

Record 51 of 113 - MEDLINE EXPRESS (R) 1994-1996

TI: Postmenopausal estrogens and progestogens and the incidence of gynecologic cancer.

AU: Weiss-NS; Hill-DA
SO: Maturitas. 1996 Mar; 23(2): 235-9
ISSN: 0378-5122
LA: ENGLISH
AN: 96353230

Record 52 of 113 - MEDLINE EXPRESS (R) 1994-1996
TI: The risk of ovarian cancer after treatment for infertility.
AU: Bristow-RE; Karlan-BY
SO: Curr-Opin-Obstet-Gynecol. 1996 Feb; 8(1): 32-7
ISSN: 1040-872X
LA: ENGLISH
AN: 96260572

Record 53 of 113 - MEDLINE EXPRESS (R) 1994-1996
TI: Re: Population-based study of tamoxifen therapy and subsequent ovarian, endometrial, and breast cancers [letter; comment]
AU: Laderoute-MP
SO: J-Natl-Cancer-Inst. 1996 Feb 21; 88(3-4): 210-1
ISSN: 0027-8874
LA: ENGLISH
AN: 96231938

Record 54 of 113 - MEDLINE EXPRESS (R) 1994-1996
TI: Ovarian tumors in postmenopausal breast cancer patients treated with tamoxifen [see comments]
AU: Cohen-I; Beyth-Y; Tepper-R; Shapira-J; Zalel-Y; Figer-A; Cordoba-M; Yigael-D; Altaras-MM
SO: Gynecol-Oncol. 1996 Jan; 60(1): 54-8
ISSN: 0090-8258
LA: ENGLISH
AN: 96139375

Record 55 of 113 - MEDLINE EXPRESS (R) 1994-1996
TI: Human menopausal gonadotropin and the risk of epithelial ovarian cancer.
AU: Shushan-A; Paltiel-O; Iscovich-J; Elchalal-U; Peretz-T; Schenker-JG
SO: Fertil-Steril. 1996 Jan; 65(1): 13-8
ISSN: 0015-0282
LA: ENGLISH
AN: 96109026

Record 56 of 113 - MEDLINE EXPRESS (R) 1994-1996
TI: Fertility drugs and breast and ovarian cancer [letter; comment]
AU: Rossing-MA; Weiss-NS
SO: Lancet. 1995 Dec 16; 346(8990): 1627-8
ISSN: 0140-6736
LA: ENGLISH
AN: 96106244

Record 57 of 113 - MEDLINE EXPRESS (R) 1994-1996
TI: Routine management of the woman on HRT [letter; comment]
AU: O'Connor-R
SO: Ir-Med-J. 1995 Sep-Oct; 88(5): 174
ISSN: 0332-3102
LA: ENGLISH
AN: 96058955

Record 58 of 113 - MEDLINE EXPRESS (R) 1994-1996
TI: Synchronous endometrial and ovarian cancer in young woman taking oral contraception.
AU: Fishman-A; Friedman-JA; Kaplan-AL
SO: Eur-J-Gynaecol-Oncol. 1995; 16(5): 346-8
ISSN: 0392-2936
LA: ENGLISH
AN: 96076300

Record 59 of 113 - MEDLINE EXPRESS (R) 1994-1996
TI: The effects of ovulation induction with gonadotrophins on the ovary and uterus and implications for assisted reproduction.
AU: Balen-A
SO: Hum-Reprod. 1995 Sep; 10(9): 2233-7
ISSN: 0268-1161
LA: ENGLISH
AN: 96121160

Record 60 of 113 - MEDLINE EXPRESS (R) 1994-1996
TI: Fertility drugs and breast and ovarian cancer [letter; comment]
AU: La-Vecchia-C; Negri-E; Parazzini-F; Franceschi-S
SO: Lancet. 1995 Dec 16; 346(8990): 1628
ISSN: 0140-6736
LA: ENGLISH
AN: 96106245

Record 61 of 113 - MEDLINE EXPRESS (R) 1994-1996
TI: Population-based study of tamoxifen therapy and subsequent ovarian, endometrial, and breast cancers [see comments]
AU: Cook-LS; Weiss-NS; Schwartz-SM; White-E; McKnight-B; Moore-DE; Daling-JR
SO: J-Natl-Cancer-Inst. 1995 Sep 20; 87(18): 1359-64
ISSN: 0027-8874
LA: ENGLISH

AN: 95387421
Record 62 of 113 - MEDLINE EXPRESS (R) 1994-1996
TI: Tamoxifen therapy and carcinogenic risk [editorial; comment]
AU: Powles-TJ; Hickish-T
SO: J-Natl-Cancer-Inst. 1995 Sep 20; 87(18): 1343-5
ISSN: 0027-8874
LA: ENGLISH
AN: 95387414

Record 63 of 113 - MEDLINE EXPRESS (R) 1994-1996
TI: A review of perineal talc exposure and risk of ovarian cancer.
AU: Harlow-BL; Hartge-PA
SO: Regul-Toxicol-Pharmacol. 1995 Apr; 21(2): 254-60
ISSN: 0273-2300
LA: ENGLISH
AN: 95372605

Record 64 of 113 - MEDLINE EXPRESS (R) 1994-1996
TI: Fertility therapy in the setting of a history of invasive epithelial ovarian cancer.
AU: Bandera-CA; Cramer-DW; Friedman-AJ; Sheets-EE
SO: Gynecol-Oncol. 1995 Jul; 58(1): 116-9
ISSN: 0090-8258
LA: ENGLISH
AN: 95309793

Record 65 of 113 - MEDLINE EXPRESS (R) 1994-1996
TI: Risk of ovarian cancer after treatment for infertility [letter; comment]
AU: Del-Priore-G; Robischon-K; Phipps-WR
SO: N-Engl-J-Med. 1995 May 11; 332(19): 1300; discussion 1302
ISSN: 0028-4793
LA: ENGLISH
AN: 95223339

Record 66 of 113 - MEDLINE EXPRESS (R) 1994-1996
TI: Self-reported use of antidepressants or benzodiazepine tranquilizers and risk of epithelial ovarian cancer: evidence from two combined case-control studies (Massachusetts, United States).
AU: Harlow-BL; Cramer-DW
SO: Cancer-Causes-Control. 1995 Mar; 6(2): 130-4
ISSN: 0957-5243
LA: ENGLISH
AN: 95267975

Record 67 of 113 - MEDLINE EXPRESS (R) 1994-1996
TI: Estrogen use and cancer incidence: a review.
AU: Lupulescu-A
SO: Cancer-Invest. 1995; 13(3): 287-95
ISSN: 0735-7907
LA: ENGLISH
AN: 95261978

Record 68 of 113 - MEDLINE EXPRESS (R) 1994-1996
TI: Estrogen replacement therapy and fatal ovarian cancer.
AU: Rodriguez-C; Calle-EE; Coates-RJ; Miracle-McMahill-HL; Thun-MJ; Heath-CW Jr
SO: Am-J-Epidemiol. 1995 May 1; 141(9): 828-35
ISSN: 0002-9262
LA: ENGLISH
AN: 95233393

Record 69 of 113 - MEDLINE EXPRESS (R) 1994-1996
TI: Risk of ovarian cancer after treatment for infertility [letter; comment]
AU: Shapiro-S
SO: N-Engl-J-Med. 1995 May 11; 332(19): 1301; discussion 1302
ISSN: 0028-4793
LA: ENGLISH
AN: 95223341

Record 70 of 113 - MEDLINE EXPRESS (R) 1994-1996
TI: Risk of ovarian cancer after treatment for infertility [letter; comment]
AU: Kurman-R; Wallach-EE; Zacur-HA
SO: N-Engl-J-Med. 1995 May 11; 332(19): 1301; discussion 1302
ISSN: 0028-4793
LA: ENGLISH
AN: 95223340

Record 71 of 113 - MEDLINE EXPRESS (R) 1994-1996
TI: Employment as hairdresser and risk of ovarian cancer and non-Hodgkin's lymphomas among women.
AU: Boffetta-P; Andersen-A; Lynge-E; Barlow-L; Pukkala-E
SO: J-Occup-Med. 1994 Jan; 36(1): 61-5
ISSN: 0096-1736
LA: ENGLISH
AN: 94186862

Record 72 of 113 - MEDLINE EXPRESS (R) 1994-1996
TI: Granulosa cell tumor of the ovary associated with antecedent tamoxifen use.
AU: Gherman-RB; Parker-MF; Macri-CI
SO: Obstet-Gynecol. 1994 Oct; 84(4 Pt 2): 717-9

ISSN: 0029-7844

LA: ENGLISH

AN: 97349541

Record 73 of 113 - MEDLINE EXPRESS (R) 1994-1996

TI: The risk of ovarian cancer after treatment for infertility [editorial; comment] [see comments]

AU: Whittemore-AS

SO: N-Engl-J-Med. 1994 Sep 22; 331(12): 805-6

ISSN: 0028-4793

LA: ENGLISH

AN: 94344197

Record 74 of 113 - MEDLINE EXPRESS (R) 1994-1996

TI: Cancer surveillance during HRT.

AU: Palacios-S

SO: Int-J-Fertil-Menopausal-Stud. 1994; 39 Suppl 2: 93-8

ISSN: 1069-3130

LA: ENGLISH

AN: 95179198

Record 75 of 113 - MEDLINE EXPRESS (R) 1994-1996

TI: Ovarian endometrioid carcinoma and endometriosis developing in a postmenopausal breast cancer patient during tamoxifen therapy: a case report and review of the literature.

AU: Cohen-I; Altaras-MM; Lew-S; Tepper-R; Beyth-Y; Ben-Baruch-G

SO: Gynecol-Oncol. 1994 Dec; 55(3 Pt 1): 443-7

ISSN: 0090-8258

LA: ENGLISH

AN: 95137476

Record 76 of 113 - MEDLINE EXPRESS (R) 1994-1996

TI: Biological effects of cosmetic talc.

AU: Wehner-AP

SO: Food-Chem-Toxicol. 1994 Dec; 32(12): 1173-84

ISSN: 0278-6915

LA: ENGLISH

AN: 95113401

Record 77 of 113 - MEDLINE EXPRESS (R) 1994-1996

TI: Re: "The authors reply" to Re: "Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women" [letter; comment]

AU: Shapiro-S

SO: Am-J-Epidemiol. 1994 Nov 15; 140(10): 958-9

ISSN: 0002-9262

LA: ENGLISH

AN: 95067881

Record 78 of 113 - MEDLINE EXPRESS (R) 1994-1996

TI: Dietary fat intake and risk of epithelial ovarian cancer.

AU: Risch-HA; Jain-M; Marrett-LD; Howe-GR

SO: J-Natl-Cancer-Inst. 1994 Sep 21; 86(18): 1409-15

ISSN: 0027-8874

LA: ENGLISH

AN: 94351761

Record 79 of 113 - MEDLINE EXPRESS (R) 1994-1996

TI: Ovarian tumors in a cohort of infertile women [see comments]

AU: Rossing-MA; Daling-JR; Weiss-NS; Moore-DE; Self-SG

SO: N-Engl-J-Med. 1994 Sep 22; 331(12): 771-6

ISSN: 0028-4793

LA: ENGLISH

AN: 94344190

Record 80 of 113 - MEDLINE EXPRESS (R) 1994-1996

TI: Depot-medroxyprogesterone acetate (DMPA) and cancer of the endometrium and ovary.

AU: Lumbiganon-P

SO: Contraception. 1994 Mar; 49(3): 203-9

ISSN: 0010-7824

LA: ENGLISH

AN: 94258912

Record 81 of 113 - MEDLINE EXPRESS (R) 1994-1996

TI: Estrogen replacement therapy and ovarian cancer risk [letter; comment]

AU: Parazzini-F; La-Vecchia-C; Negri-E; Villa-A

SO: Int-J-Cancer. 1994 Apr 1; 57(1): 135-6

ISSN: 0020-7136

LA: ENGLISH

AN: 94200881

Record 82 of 113 - MEDLINE EXPRESS (R) 1994-1996

TI: The estimated effect of oral contraceptive use on the cumulative risk of epithelial ovarian cancer.

AU: Gross-TP; Schlesselman-JJ

SO: Obstet-Gynecol. 1994 Mar; 83(3): 419-24

ISSN: 0029-7844

LA: ENGLISH

AN: 94173532

Record 83 of 113 - MEDLINE EXPRESS (R) 1994-1996

TI: Ovarian cancer and pregnancy: comment on a paper by Whittemore et al.
AU: Walters-DE
SO: Fertil-Steril. 1994 Feb; 61(2): 239-42
ISSN: 0015-0282
LA: ENGLISH
AN: 94131073

Record 84 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Dioxins--a commentary on gynaecological aspects of recent research.
AU: Hanf-V
SO: Arch-Gynecol-Obstet. 1993; 253(1): 1-4
ISSN: 0932-0067
LA: ENGLISH
AN: 93319303

Record 85 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Ovarian stimulation and granulosa-cell tumour [letter; comment]
AU: Goczke-PM; Freeman-DA; Arany-A; Garadnay-B
SO: Lancet. 1993 May 22; 341(8856): 1346
ISSN: 0140-6736
LA: ENGLISH
AN: 93261167

Record 86 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Ovarian stimulation and granulosa-cell tumour [letter; comment]
AU: Jansen-R
SO: Lancet. 1993 May 22; 341(8856): 1345; discussion 1345-6
ISSN: 0140-6736
LA: ENGLISH
AN: 93261166

Record 87 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Ovarian stimulation and granulosa-cell tumour [letter; comment]
AU: Evers-JL
SO: Lancet. 1993 May 22; 341(8856): 1345; discussion 1345-6
ISSN: 0140-6736
LA: ENGLISH
AN: 93261165

Record 88 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Ovulation induction agents and ovarian cancer [letter; comment]
AU: Sassoon-S
SO: Hum-Reprod. 1993 Dec; 8(12): 2246-7
ISSN: 0268-1161
LA: ENGLISH
AN: 94201345

Record 89 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Metastatic ovarian strumosis in an in-vitro fertilization patient.
AU: Balasch-J; Pahisa-J; Marquez-M; Ordi-J; Fabregues-F; Puerto-B; Vanrell-JA
SO: Hum-Reprod. 1993 Dec; 8(12): 2075-7
ISSN: 0268-1161
LA: ENGLISH
AN: 94201316

Record 90 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Fertility drugs and ovarian cancer. International Federation of Fertility Societies (IFFS)
SO: Fertil-Steril. 1993 Sep; 60(3): 406-8
ISSN: 0015-0282
LA: ENGLISH
AN: 93387492

Record 91 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Hemorrhagic ovarian cysts in patients on anticoagulation therapy: CT findings.
AU: Wilbur-AC; Goldstein-LD; Prywitch-BA
SO: J-Comput-Assist-Tomogr. 1993 Jul-Aug; 17(4): 623-5
ISSN: 0363-8715
LA: ENGLISH
AN: 93322524

Record 92 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Hormone replacement therapy and malignancy.
AU: Fitzgerald-CT; Elstein-M; Mansel-RE
SO: Br-J-Obstet-Gynaecol. 1993 May; 100(5): 408-10
ISSN: 0306-5456
LA: ENGLISH
AN: 93298712

Record 93 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Fertility drugs and ovarian cancer: red alert or red herring--new information [letter; comment]
AU: Darder-MC
SO: Fertil-Steril. 1993 Jul; 60(1): 199-201
ISSN: 0015-0282
LA: ENGLISH
AN: 93292716

Record 94 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Hormone replacement therapy and cancer.

AU: Mack-TM

SO: Baillieres-Clin-Endocrinol-Metab. 1993 Jan; 7(1): 113-49

ISSN: 0950-351X

LA: ENGLISH

AN: 93168081

Record 95 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Fertility drugs and ovarian cancer: red alert or red herring? [see comments]

AU: Spirtas-R; Kaufman-SC; Alexander-NJ

SO: Fertil-Steril. 1993 Feb; 59(2): 291-3

ISSN: 0015-0282

LA: ENGLISH

AN: 93146178

Record 96 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Relationship of hormone use to cancer risk.

AU: Bernstein-L; Ross-RK; Henderson-BE

SO: J-Natl-Cancer-Inst-Monogr. 1992(12): 137-47

ISSN: 1052-6773

LA: ENGLISH

AN: 92313754

Record 97 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Effects of hormone replacement therapy.

AU: Crosignani-PG

SO: Int-J-Fertil. 1992; 37 Suppl 2: 98-103

ISSN: 0020-725X

LA: ENGLISH

AN: 92372247

Record 98 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Postmenopausal endometrioma and hormonal replacement therapy.

AU: Goh-JT; Hall-BA

SO: Aust-N-Z-J-Obstet-Gynaecol. 1992 Nov; 32(4): 384-5

ISSN: 0004-8666

LA: ENGLISH

AN: 93176086

Record 99 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Hormone replacement and cancer.

AU: Barrett-Connor-E

SO: Br-Med-Bull. 1992 Apr; 48(2): 345-55

ISSN: 0007-1420

LA: ENGLISH

AN: 93082377

Record 100 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Borderline malignancy of the ovary and controlled hyperstimulation, a report of 2 cases.

AU: Nijman-HW; Burger-CW; Baak-JP; Schats-R; Vermorken-JB; Kenemans-P

SO: Eur-J-Cancer. 1992; 28A(12): 1971-3

ISSN: 0959-8049

LA: ENGLISH

AN: 93040603

Record 101 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: The risk of epithelial ovarian cancer in short-term users of oral contraceptives.

AU: Gross-TP; Schlesselman-JJ; Stadel-BV; Yu-W; Lee-NC

SO: Am-J-Epidemiol. 1992 Jul 1; 136(1): 46-53

ISSN: 0002-9262

LA: ENGLISH

AN: 93035222

Record 102 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Mineral fiber exposure and the development of ovarian cancer.

AU: Rosenblatt-KA; Szklo-M; Rosenshein-NB

SO: Gynecol-Oncol. 1992 Apr; 45(1): 20-5

ISSN: 0090-8258

LA: ENGLISH

AN: 92290319

Record 103 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Ovulation and ovarian cancer [letter; comment]

AU: Dietl-J

SO: Lancet. 1991 Aug 17; 338(8764): 445

ISSN: 0140-6736

LA: ENGLISH

AN: 91325760

Record 104 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Tamoxifen to prevent breast cancer [letter]

AU: Baum-M; Houghton-J; Riley-D

SO: Lancet. 1991 Jul 13; 338(8759): 114

ISSN: 0140-6736

LA: ENGLISH

AN: 91287397

Record 105 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Ovarian cancer and long-term tamoxifen in premenopausal women [letter]
AU: Spicer-DV; Pike-MC; Henderson-BE
SO: Lancet. 1991 Jun 8; 337(8754): 1414
ISSN: 0140-6736
LA: ENGLISH
AN: 91245885

Record 106 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Epidemiologic data on exogenous hormones and hepatocellular carcinoma and selected other cancers.
AU: Prentice-RL
SO: Prev-Med. 1991 Jan; 20(1): 38-46
ISSN: 0091-7435
LA: ENGLISH
AN: 91180051

Record 107 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Depot-medroxyprogesterone acetate (DMPA) and risk of epithelial ovarian cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives.
SO: Int-J-Cancer. 1991 Sep 9; 49(2): 191-5
ISSN: 0020-7136
LA: ENGLISH
AN: 91348923

Record 108 of 113 - MEDLINE EXPRESS (R) 1991-1993

TI: Oral contraceptives and reproductive system cancer. Benefits and risks.
AU: Williams-JK
SO: J-Reprod-Med. 1991 Mar; 36(3 Suppl): 247-52
ISSN: 0024-7758
LA: ENGLISH
AN: 91259532

Record 109 of 113 - MEDLINE EXPRESS (R) 1986-1990

TI: Role of prolonged excessive estrogen stimulation in the pathogenesis of endometrial sarcomas: two cases and a review of the literature.
AU: Altaras-MM; Jaffe-R; Cohen-I; Gruber-A; Yanai-Inbar-I; Bernheim-J
SO: Gynecol-Oncol. 1990 Aug; 38(2): 273-7
ISSN: 0090-8258
LA: ENGLISH
AN: 90353843

Record 110 of 113 - MEDLINE EXPRESS (R) 1986-1990

TI: Follicular and luteal cysts after treatment with gonadotropin-releasing hormone analog for in vitro fertilization.
AU: Ben-Rafael-Z; Bider-D; Menashe-Y; Maymon-R; Zolti-M; Mashiach-S
SO: Fertil-Steril. 1990 Jun; 53(6): 1091-4
ISSN: 0015-0282
LA: ENGLISH
AN: 90276669

Record 111 of 113 - MEDLINE EXPRESS (R) 1986-1990

TI: Methylxanthine consumption and the risk of ovarian malignancy.
AU: Leviton-A
SO: Cancer-Lett. 1990 May 30; 51(2): 91-101
ISSN: 0304-3835
LA: ENGLISH
AN: 90263049

Record 112 of 113 - MEDLINE EXPRESS (R) 1986-1990

TI: Re: "Triazine herbicides and ovarian epithelial neoplasms" by A Donna, P Crosignani, F Robutti, PG Betta, R Bocca, N Mariani, F Ferrario, R Fissi, F Berrino Scand J Work Environ Health 1989 [letter; comment]
AU: Minder-CE
SO: Scand-J-Work-Environ-Health. 1990 Dec; 16(6): 445-7
ISSN: 0355-3140
LA: ENGLISH
AN: 91134670

Record 113 of 113 - MEDLINE EXPRESS (R) 1986-1990

TI: Epidemiologic aspects of early menopause and ovarian cancer.
AU: Cramer-DW
SO: Ann-N-Y-Acad-Sci. 1990; 592: 363-75; discussion 390-4
ISSN: 0077-8923
LA: ENGLISH
AN: 90328634

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		OPDRA POSTMARKETING SAFETY REVIEW	
TO: Lilia Talarico, M.D., Director Division of Gastrointestinal and Coagulation Drug Products, HFD-180		FROM: Ann Corken Mackey, RPh, MPH Safety Evaluator Division of Drug Risk Evaluation II (DDREII) HFD-440	OPDRA PID # 010176 APR 10 2001
DATE REQUESTED: April 3, 2001	REQUESTOR/Phone #:		
DATE RECEIVED:			
DRUG (Est): Cisapride (Propulsid) Methyldopa (Aldomet) Bethanechol (Urecholine)	NDA/IND # 20210, 13400, 21200	SPONSOR:	
DRUG NAME (Trade):		THERAPEUTIC CLASSIFICATION:	
EVENT: AERS reports associated with increased frequency of abdominal or pelvic surgery			
Executive Summary: This consult was prepared in response to a request from HFD-180 dated April 3, 2001. Because of safety concerns related to the use of tegaserod hydrogen maleate, HFD-180 requested an Adverse Event Reporting System (AERS) search of other prokinetic agents (specifically cisapride, methyldopa, _____ and bethanechol) that are associated with increased frequency of abdominal or pelvic surgery, especially cholecystectomy and appendectomy.			
A search of AERS identified four cases of cholecystectomy (including one patient who also had a herniorrhaphy) associated with cisapride use. The primary focus of these reports was the patients' cardiac events associated with cisapride use; they provided no information about the patients' cholecystectomies/herniorrhaphy. In addition, one of these patients had a pre-existing chronic cholecystitis and took only one to three doses of cisapride; two of these reports were submitted by consumers, so the information was not of high quality. The AERS search identified no cases of abdominal or pelvic surgery associated with the use of methyldopa, _____ or bethanechol. A search of the medical literature identified no cases of abdominal or pelvic surgery associated with the use of these agents.			
Based on limited findings in the AERS database and the medical literature, we cannot make any conclusions about prokinetic agents (specifically cisapride, methyldopa, _____ bethanechol) and an increase in frequency of abdominal or pelvic surgery. We will continue to monitor these drugs closely for such events.			
Reason for Request/Review: HFD-180 has concerns about safety issues related to the use of tegaserod hydrogen maleate and has requested a search of other prokinetic agents (specifically cisapride, methyldopa, _____ and bethanechol) that are associated with increased frequency of abdominal or pelvic surgery, especially cholecystectomy and appendectomy.			
Relevant Product Labeling: The product labels for cisapride, methyldopa, _____ (not marketed in the U.S.), and bethanechol do not mention an increased frequency of abdominal or pelvic surgery.			
Search Date: April 4, 2001	Search Type(s): AERS Literature		
Search Criteria: Drug Names: Cisapride (Propulsid), Methyldopa (Aldomet), _____, Bethanechol (Urecholine)			
MedDRA Terms: High Level Group Terms (HLGTs) <i>Gastrointestinal operations and other therapeutic procedures</i> and <i>hepatobiliary operations</i> for cisapride System Organ Class term (SOC) <i>Surgical & medical procedures</i> for methyldopa, _____, and bethanechol.			

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Search Results: The searches produced the following results: cisapride (8 unduplicated reports), methyldopa (29 reports), _____ and bethanechol (6 reports). Note that a search using cisapride and SOC *Surgical & medical procedures* produced 114 reports, so the search was narrowed as specified above. There were 8 unduplicated reports for cisapride; 5 reports involved cholecystectomy (including one patient who also had a herniorrhaphy) and will be discussed in detail below. The 3 remaining reports for cisapride involved the following: one banded gastroplasty for morbid obesity, one death from intestinal perforation and/or diac arrhythmia, and one surgical intervention for esophageal dilations. In reviewing the 29 reports for methyldopa, only one report involved abdominal or pelvic surgery; that report was for surgical repair of a small bowel obstruction caused by undissolved Procardia XL tablets. Of the _____ and the 6 reports for bethanechol, none involved abdominal or pelvic surgery.

The search produced 5 cases of cholecystectomy associated with cisapride use. One consumer report has been excluded because when the drug company followed up with the patient's physician, it appeared that cisapride was not listed in the medical records. The remaining 4 reports are summarized below.

FDA# 3355112 (Mfr# — USA1999002448) (USA, 1999) A 66-year-old female was hospitalized for heart palpitations after taking 30 mg of cisapride a day for 11 months to treat GERD. She also stated that she was hospitalized for a cholecystectomy after taking cisapride for approximately 7 months. Concomitant medications included clonazepam and losartan; she had essential hypertension. This report was submitted by a consumer; very little information was provided.

FDA# 3152946 (Mfr# — USA-17189) (USA, 1995) A 70-year-old male required a cholecystectomy due to chronic cholecystitis 12 days after taking only one to three doses of cisapride to treat a hiatal hernia. The focus of this report was the cardiac event the patient experienced (Torsades de Pointes which progressed to ventricular fibrillation) while taking cisapride; no information was provided about the cholecystectomy. The patient eventually died of prostate cancer. Concomitant medications included doxazosin, ranitidine, and coumadin; his medical history also included cardiomyopathy, bundle branch block, atrial fibrillation, gastritis, and hypertension.

FDA# 3463931 (Mfr# — USA2000002694) (USA, 2000) A 56-year-old female developed cardiac problems during laparoscopic cholecystectomy for cholelithiasis and cholecystitis; she had taken 40 mg of cisapride a day for 135 days to treat dyspepsia. This report was submitted by a consumer; the follow up physician was not the provider for the patient's cholecystectomy, but stated that the patient had an abnormal EKG. Concomitant medications included amitriptyline, lansoprazole, amlodipine, valsartan, sucralfate, and Prempro; her medical history included obesity, jaundice, Hepatitis A, vagotomy, pyloroplasty, asthma, osteoarthritis, myositis, and arthropathy.

A# 3476565 (Mfr# — USA2000000419) (USA, 1997) A 41-year-old female had been taking cisapride (40 to 60 mg a day) since 1993 to treat "diabetes with neurological." In 1997, the patient developed sinus bradycardia and second degree sinoatrial node block with first degree atrioventricular block; it also was reported that she had a cholecystectomy in 1996 and a herniorrhaphy both of umbilicus and right inguinal site in 1997. The focus of this report was on the patient's cardiac events; no information was provided about the cholecystectomy or herniorrhaphy. The patient's medical history and list of concomitant medications were too extensive to include.

A search of the medical literature on April 4, 2001 produced no cases of abdominal or pelvic surgery associated with the use of cisapride, methyldopa, _____, or bethanechol.

Discussion / Conclusions: This consult was prepared in response to a request from HFD-180 dated April 3, 2001. Because of safety concerns related to the use of tegaserod hydrogen maleate, they requested an Adverse Event Reporting System (AERS) search of other prokinetic agents (specifically cisapride, methyldopa, _____ and bethanechol) that are associated with increased frequency of abdominal or pelvic surgery, especially cholecystectomy and appendectomy.

A search of AERS identified four cases of cholecystectomy (including one patient who also had a herniorrhaphy) associated with cisapride use. The primary focus of these reports was the patients' cardiac events associated with cisapride use; they provided no information about the patients' cholecystectomies/herniorrhaphy. In addition, one of these patients had a pre-existing chronic cholecystitis and took only one to three doses of cisapride; two of these reports were submitted by consumers, so the information was not of high quality. The AERS search identified no cases of abdominal or pelvic surgery associated with the use of methyldopa, _____ or bethanechol. A search of the medical literature identified no cases of abdominal or pelvic surgery associated with the use of these agents.

Based on limited findings in the AERS database and the medical literature, we cannot make any conclusions about prokinetic agents (specifically cisapride, methyldopa, _____ bethanechol) and an increase in frequency of abdominal or pelvic surgery. We will continue to monitor these drugs closely for such events.

Reviewer's Signature / Date: 4/10/01

Acting Division Director Signature / Date: 10 April 2001 (for K. Hall)

Team Leader's Signature / Date: 4/10/01

Cc: NDA # 20210, 13400, 21200

HFD-180 Division File/Talarico / MO / SMO / Project Manager

HFD-440/Uhl/Dempsey/Green/Chron/Drug

**APPEARS THIS WAY
ON ORIGINAL**

Team Leader Memorandum

To: Paul E. Levine, Jr. (HFD-180)

From: Dena R. Hixon, M.D. (HFD-580)

Re: Controlled Correspondence DRUDP- 019
Request for consultation re NDA 21-200, Zelmec (tegaserod) and Ovarian Cysts

Date: April 18, 2000

Background

NDA 21-200 is presented by Novartis Pharms for Zelmec (tegaserod hydrogen maleate 2/6 mg) for the treatment of irritable bowel syndrome (IBS) in patients who identify _____
_____ constipation as their predominant symptoms.

Clinical review of this NDA revealed GI disorders to be the most commonly reported AEs in the target population. Only diarrhea was clearly identified as occurring more frequently in tegaserod-treated patients compared with placebo-treated patients, and this was not unexpected considering the pharmacodynamic profile of the drug. The most common other AEs were headache and other GI disorders.

SAEs were infrequent, 1.8% in both tegaserod and placebo patients in phase 2/3 studies, and 4.1% in long-term studies. There were a total of five cases of ovarian cyst requiring surgery in the tegaserod patients and none in the placebo patients. Overall, there were nine cases of ovarian cyst reported as AEs, both serious and non-serious, of which eight were in tegaserod patients.

Reports of Ovarian Cysts

1. B209/11/39, a 50-year-old white woman with a history of meno-metrorrhagia and ovarian cyst for 10 years prior to the study, asymptomatic with no change during the study, underwent elective surgery after 334 days of study participation, planned beforehand. She developed peritonitis as a post-operative complication. The cyst was described as a "water cyst", and the pathology was benign.
Comment: This SAE is clearly unrelated to the study drug, as it is a pre-existing condition with no worsening of condition during the study according to the investigator. However, it would be helpful to know the size of the cyst.
2. B209/26/6, a 45-year-old white woman with a previous hysterectomy presented with pain. CT scan, ultrasound, and barium enema were inconclusive but indicated that adhesions were the most likely cause of her pain, and she underwent bilateral salpingo-oophorectomy after 261 days on the study drug. The post-operative diagnosis was adhesions between gut and omentum to the left pelvic wall and ovary and stress urinary incontinence. There was no mention of a cyst and no pathology request.
Comment: This SAE was not associated with an ovarian cyst.
3. B209/28/4, a 35-year-old woman underwent a hysterectomy and right salpingo-oophorectomy after 306 days on the study drug. The pathology report revealed multiple ovarian cysts, including a 3.5 cm partially luteinized follicle cyst and focal adenomyosis of the uterus.
Comment: This is consistent with a functional ovarian cyst.
4. B209/28/22, a 40-year-old white woman with a history of dysmenorrhea experienced right lower abdominal pain after 89 days on the study drug and was presumptively diagnosed with a ruptured ovarian cyst without any diagnostic procedures.
Comment: There is no objective evidence of an ovarian cyst as the cause of this AE.
5. B251/32/2, a 22-year-old white woman was diagnosed with a polycystic ovary after 43 days of study drug. No treatment was specified, and no further clinical information provided.

Comment: It would be helpful to acquire further information about this patient, including the size of her ovaries and the size of the largest cyst present, and clinical information regarding menstrual pattern, any history of infertility or previous pregnancies, and any evidence of hyperandrogenism. Polycystic Ovarian Syndrome is a discreet entity that usually involves enlarged ovaries with multiple small (<1cm) cysts. Patients usually experience infrequent, irregular menstrual cycles and frequently have infertility, episodic abdominal pain, obesity, hyperinsulinemia, and hirsutism. If, this patient exhibits such findings, her condition would not likely be related to the study drug.

6. B251/32/7, a 30-year-old white woman with a history of dysmenorrhea at the beginning of the study was discovered at gynecology consultation a month later to have an ovarian cyst after 56 days of study drug. It evolved with the menstrual cycle, and no specific treatment was given.

Comment: This is the typical clinical history of a functional ovarian cyst. It would be helpful to acquire further information about size of the cyst and how it was diagnosed (by examination or ultrasound).

7. B301/163/10, a 23-year-old white woman who received placebo presented after 71 days with abdominal pain and was diagnosed with polycystic ovaries by CT scan. She was treated with Meloden, an oral contraceptive.

Comment: see #5 above

8. B307/721/2, a 37-year-old black woman with previous hysterectomy presented after 100 days of study drug with pain associated with a 2.7 cm right ovarian cyst seen on CT scan. The pain attenuated somewhat with apparent spontaneous rupture but persisted with reappearance of the cyst, unrelieved with Danocrine treatment. A right salpingo-oophorectomy, lysis of pelvic adhesions, and appendectomy were performed 5-6 weeks after the initial cyst was seen. Pathology revealed a 1 cm benign peritubal cyst, ovarian/fallopian tube adhesions, and normal appendix.

Comment: There was no evidence of an ovarian cyst on pathology report or operative report. She may have had a small functional cyst at the time of the initial CT scan, or the peritubal cyst may have appeared to be an ovarian cyst.

9. B351/518/27, a 13-year-old white girl with previous resection of bilateral ovarian cysts presented after 87 days of study drug with right abdominal pain. She underwent laparoscopic resection of a right ovarian cyst and appendix. Her pathology report revealed early acute appendicitis. A 4-5 cm simple cyst was noted intraoperatively.

Comment: This is the clinical history of recurrent functional cysts in a young woman near the age of menarche.

Summary of cases

Three of the above 9 cases can clearly be excluded because one (#1) was pre-existing, and there was no documentation of a cyst for the other 2 (#2 and #4). Documentation is inadequate for another 3 (#5, 6, and 7). At most, this represents 5 ovarian cysts in the tegaserod group (N=1649) and one in the placebo group (N=607), giving an estimated frequency of 0.3% of tegaserod users or 898 (95% CI = 296-2103) per 100,000 woman-years for tegaserod and 0.1% of placebo users or 734 (95% CI = 0-4057) per 100,000 woman-years for placebo. Three cases resulted in hospitalization and surgical intervention in the tegaserod group vs. none in the placebo group. The confidence intervals for these events in the tegaserod and placebo groups are wide and overlapping, and they do not show a statistically significant difference.

Discussion of Ovarian Cysts

There is no information available regarding the overall incidence of ovarian cysts in the general population. However, hospital discharge data reveals an incidence of 500/100,000 hospital discharges from 1979 to 1986 and 327/100,000 discharges from 1988 to 1990. The incidence of cysts not requiring intervention can be expected to be significantly higher.

The majority of ovarian cysts are functional in nature, resulting from aberrations in ovulatory menstrual cycles. When, during the first half of the menstrual cycle, the dominant follicle does not succeed in ovulating and remains active but immature, or if any of the less-stimulated follicles fail to undergo their normal atresia, one or more follicle cysts may develop. Usually, they remain small, averaging only 1.0 to 1.5 cm in diameter, but occasionally a solitary one may attain the size of a small lemon (6 to 8 cm in diameter). They invariably disappear spontaneously, either by slow resorption of fluid or by sudden rupture. Rupture of a follicle cyst or, occasionally, torsion of the ovary containing it may give rise to transient acute or chronic intermittent lower abdominal pain. In most instances, however, conservative management suffices, and the ovary returns to normal size, with subsidence of any associated symptoms, usually within a month or two.¹

These functional ovarian cysts commonly occur as a complication of drugs used for ovulation induction and with some progestin-containing contraceptives and Tamoxifen. The incidence of ovarian cysts in pre-approval studies of Clomiphene, a relatively mild ovulation induction drug, was 13%. A search of the PDR for "ovarian cysts" showed 44 drugs out of 2306 searched, and only 4 of these were not reproductive drugs:

Serevent, an asthma drug was associated with ovarian cysts in mice.

Avonex, an interferon drug for multiple sclerosis was associated with a 3% incidence of ovarian cysts vs. 0 % in controls.

Copaxone, for multiple sclerosis, was associated with ovarian cysts in 1/100-1/1000

Effexor, an antidepressant, associated with ovarian cysts in less than 1/1000

Most drug-induced cysts are functional cysts and will resolve spontaneously within one or two menstrual cycles. They can be managed conservatively with discontinuation of the drug, analgesics, and observation.

Recommendations

Given the available information regarding the occurrence of ovarian cysts in the clinical studies of Zelmac, a causal relationship is not clear. The most common presenting symptom of ovarian cysts is abdominal or pelvic pain, which is also common in the population of patients with Irritable Bowel Syndrome. Whereas functional cysts usually resolve spontaneously and usually do not require surgical intervention, this AE can be adequately addressed in product labeling and should not be an approvability issue.

/S/
Dena R. Hixon, M.D., FACOG
Acting Team Leader, DRUDP

**APPEARS THIS WAY
ON ORIGINAL**

¹ Green, Thomas H, Jr, M.D., *Gynecology: Essentials of Clinical Practice*, 3rd Edition, Little, Brown and Company, Boston, 1977

MEMORANDUM OF TELECON

DATE: JULY 18, 2002

APPLICATION NUMBER: NDA 21-200, Zelnorm™ (tegaserod) Tablets

BETWEEN:

Novartis Pharmaceuticals Corporation

Martin Lefkowitz, M.D., Executive Director, Clinical Research & Development

David Earnest, M.D., Clinical Research Physician, Clinical Research & Development

Mathias Hukkelhoven, Ph.D., U.S. Head of Regulatory Affairs

Donna Vivelo, Associate Director, Drug Regulatory Affairs

Phone: (973) 781-3572

Representing: Novartis Pharmaceuticals Corporation

AND

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Joyce Korvick, M.D., M.P.H., Deputy Director

Paul E. Levine, Jr., R.Ph., Regulatory Project manager

SUBJECT: To discuss issues related to the action for Zelnorm, NDA 21-200.

BACKGROUND:

On February 11, 2000, Novartis Pharmaceuticals Corporation, submitted NDA 21-200 for the treatment of _____

in patients with irritable bowel syndrome (IBS) who identify _____
_____ constipation as their predominant symptoms".

In a letter dated August 11, 2000, the Agency notified the sponsor that the new drug application was approvable because of concerns about the efficacy and safety of the drug. On December 15, 2000, the sponsor submitted a complete response to this approvable letter.

In a letter dated June 15, 2001, the Agency notified the sponsor that after review of the December 15, 2000, resubmission, the application was not approvable because the safety concerns for use of tegaserod outweighed the drug's effect.

On February 28, 2002, following discussions with Agency, the sponsor submitted a complete response to the June 15, 2001 not approvable letter. This response contained

additional safety data, a proposal for a risk management program, and revised labeling for Zelnorm.

On June 19 and 26; and July 03, 10, and 16, 2002, the Agency met with the sponsor to discuss issues concerning the review of the application and sponsor's proposed labeling for Zelnorm.

THE CALL:

Dr. Korvick stated that the Agency requests Novartis to submit reported adverse events for abdominal and pelvic surgeries as Postmarketing 15-day Safety Reports.

The sponsor asked if the Agency would accept receiving quarterly summary reports instead of the 15-day reports, and whether the reports should include all abdominal and pelvic surgeries. The sponsor stated that quarterly safety report summaries would allow Novartis an opportunity to adequately process and evaluate the contents of the safety reports.

Dr. Korvick stated that the sponsor should submit postmarketing 15-day safety reports on all adverse events of abdominal and pelvic surgeries, at least, for the immediate future or until the Agency is able to adequately assess the safety profile of Zelnorm in the postmarketing phase. Dr. Korvick further stated that the Agency intends to include a statement about the adverse events reporting in the action letter and would reconsider the appropriateness of the 15-day reporting when more is known about the postmarketing safety profile of the drug.

The sponsor agreed to provide 15-day reports of abdominal and pelvic surgeries as requested by the Agency, but stated that it would have to coordinate the reporting process with Novartis' international constituents. The sponsor asked that the Agency also include in the action letter a statement that a meeting would be held to reassess the need for these reports.

Dr. Korvick agreed to the request and informed the sponsor that if a safety signal were identified in postmarketing adverse event reports for Zelnorm, the risk of the drug would outweigh its benefit under the current indication.

[The sponsor was informed that this recommendation is consistent with the advice received from the Advisory and Consultant Staff in the June 26, 2000, Gastrointestinal Advisory Committee Meeting.]

The sponsor asked if the Agency recommends studies for _____

Dr. Korvick stated that the sponsor should include studies

[

]

Dr. Korvick informed the sponsor that the Agency would be willing to discuss the matter further, as desired.

The sponsor stated that it would consider the Agency's comments.

Dr. Korvick informed the sponsor that the action letter would include a deferral of pediatric studies for at least 2 years. The Agency would have future discussions with Novartis about the appropriateness of studies in the pediatric population after the risks associated with use of Zelnorm have been clearly defined.

The call was ended

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Paul Levine
7/26/02 02:07:03 PM
CSO

Joyce Korvick
7/27/02 02:09:51 PM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELECON

DATE: JULY 10, 2002

APPLICATION NUMBER: NDA 21-200, Zelnorm™ (tegaserod) Tablets

BETWEEN:

Novartis Pharmaceuticals Corporation

Martin Lefkowitz, M.D., Executive Director, Clinical Research & Development

David Earnest, M.D., Clinical Research Physician, Clinical Research &
Development

James McLeod, MD, Executive Director, Clinical Pharmacology

Jean J Garaud, Global Head of CRD

Kurt Graves, Senior Vice-President and General Manager, US Commercial
Operations

Mathias Hukkelhoven, Ph.D., U.S. Head of Regulatory Affairs

Donna Vivello, Associate Director, Drug Regulatory Affairs

Phone: (973) 781-3572

AND

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Victor Raczkowski, M.D., M.Sc., Acting Director

Joyce Korvick, M.D., M.P.H., Deputy Director

Hugo E. Gallo-Torres, M.D., Ph.D., Medical Team Leader, GI Drugs

Gary J. Della'Zanna, D.O., M.Sc., Medical Reviewer

Liang Zhou, Ph.D., Chemistry Team Leader

Paul E. Levine, Jr., R.Ph., Regulatory Project manager

Office of Drug Evaluation III (HFD-103)

Florence Houn, M.D., M.P.H., Director

Office of Clinical Pharmacology and Biopharmaceutics (OCPB), HFD-870

Suliman Al-Fayoumi, Ph.D., Biopharm Reviewer

Division of Biometrics II (HFD-715)

Edward Nevius, Ph.D., Division Director

Tom Permutt, Ph.D., Statistical Team Leader

Division of Surveillance, Research, and Communication Support, HFD-410

Jeanine Best, MSN, RN, PNP, Regulatory Health Project Manager

Division of Drug Marketing, Advertising, and Communications, HFD-42

Marci Kiester, Pharm.D., Senior Regulatory Review Officer

SUBJECT: To answer the sponsor's questions concerning the Agency's comments on the sponsor's proposed labeling.

BACKGROUND:

On February 11, 2000, Novartis Pharmaceuticals Corporation, submitted NDA 21-200 for the treatment of _____ in patients with irritable bowel syndrome (IBS) who identify _____ constipation as their predominant symptoms".

In a letter dated August 11, 2000, the Agency notified the sponsor that the new drug application was approvable. After reviewing the sponsor's response to the Approvable Letter, the Agency notified the sponsor in a letter dated June 15, 2001, that the application was not approvable.

On February 28, 2002, following discussions with the Agency, the sponsor submitted a complete response to the June 15, 2001 not approvable letter. This response contained additional safety data, a proposal for a risk management program, and revised labeling.

On June 19 & 26, and July 03, 2002, the Agency met with the sponsor to discuss issues concerning the review of the application and proposed labeling for Zelnorm™.

On July 09, 2002, the sponsor submitted draft labeling in response to the Agency's comments in the July 03, 2002, meeting.

THE CALL:

The sponsor's draft labeling, submitted July 09, 2002, was used as a reference for discussion in this meeting (see attachment).

LABELING DISCUSSION

The sponsor was informed that the proposed revisions to the Prescribing Information insert were acceptable, except for the following.

Under the CLINICAL STUDIES section, the Agency recommended the deletion of the statement on lines 129-131,

{

}

The sponsor agreed to the Agency's request to delete the lines.

Under the CLINICAL STUDIES section, the Agency recommended that the sponsor either provide a responder analysis in support of or delete the statement beginning on line 141, ' [

As a rationale, FDA indicated that these changes in mean data are of unclear clinical significance for individual patients. However, the data could be expressed in a way that is more clinically meaningful by performing a responder analysis and showing that the effects of Zelnorm can be differentiated from placebo. For example, responders could be defined as patients who had sustained improvement scores for abdominal pain/discomfort and bloating or as patients who had sustained improvement in their symptoms of constipation.

The sponsor indicated that the purpose of the proposed statement is to provide information to the physician about the beneficial effects of Zelnorm. The sponsor stated that although additional analyses are not available at this time, performance scales and what was measured could be added to clarify the statement. The sponsor asked what is the Agency's concern about the statement.

The Agency expressed its concern that the current language provides no significant benefit to the physician. In addition, the Agency expressed its concern about the potential marketing implications of claims for secondary endpoints that are not supported by data such as responder analyses.

The sponsor stated that the primary endpoint would be the major component of the marketing plan for Zelnorm. The sponsor agreed to consider the Agency's comments and to submit a responder analysis. The sponsor asked if the Agency would review this analysis as quickly as possible.

The Agency agreed to expeditiously review the responder analysis when submitted.

The following requests concerning the proposed patient package insert were conveyed to the sponsor.

1. Revise the format of the patient package insert to be consistent with the format required for Medications Guides under 21 CFR §208.20
2. Change lines 6-8 under the section, INFORMATION FOR THE PATIENT:

From:

[

]

[]

To:

"Read this information carefully before you start taking ZELNORM (ZEL-norm).
Read the information you get each time you get more ZELNORM. There may be
new information. This information does not take the place of talking to your
doctor about your medical condition or treatment."

3. Delete the section, _____
4. Change lines 20-22 under the section, WHAT IS ZELNORM?:

From:

[]

To:

[]

5. Under the section, WHAT IS ZELNORM?, delete lines 23-26:

[]

6. Under the section, WHAT ARE THE POSSIBLE SIDE EFFECTS OF ZELNORM?,
delete lines 68-70:

[]

GENERAL DISCUSSION

The sponsor was informed that the proposed Phase-4 commitments, submitted July 09, 2002, were acceptable.

Labeling Attachment:

**Confidential –
Not For Public Disclosure**

**APPEARS THIS WAY
ON ORIGINAL**

WITHHOLD 15 PAGE (S)

Draft

Labeling

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Paul Levine
7/26/02 02:03:53 PM
CSO

Joyce Korvick
7/27/02 02:05:50 PM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELECON

DATE: JULY 03, 2002

APPLICATION NUMBER: NDA 21-200, Zelnorm™ (tegaserod) Tablets

BETWEEN:

Novartis Pharmaceuticals Corporation

Martin Lefkowitz, M.D., Executive Director, Clinical Research & Development

David Earnest, M.D., Clinical Research Physician, Clinical Research &
Development

Bo Joelsson, M.D., Global Therapeutic Area Head, Gastroenterology

Kurt Graves, Senior Vice-President and General Manager, US Commercial
Operations

Mathias Hukkelhoven, Ph.D., U.S. Head of Regulatory Affairs

Phillip Bently, Ph.D., Preclinical Safety

Donna Vivelo, Associate Director, Drug Regulatory Affairs

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AND

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Joyce Korvick, M.D., M.P.H., Deputy Director

Liang Zhou, Ph.D., Chemistry Team Leader

Paul E. Levine, Jr., R.Ph., Regulatory Project manager

Office of Drug Evaluation III (HFD-103)

Florence Houn, M.D., M.P.H., Director

Office of Clinical Pharmacology and Biopharmaceutics (OCPB), HFD-870

Suliman Al-Fayoumi, Ph.D., Biopharm Reviewer

Division of Biometrics II (HFD-715)

Edward Nevius, Ph.D., Division Director

Tom Permutt, Ph.D., Statistical Team Leader

Division of Drug Marketing, Advertising, and Communications, HFD-42

Marci Kiester, Pharm.D., Senior Regulatory Review Officer

SUBJECT: To discuss issues related to review of the labeling for Zelnorm.

BACKGROUND:

On February 11, 2000, Novartis Pharmaceuticals Corporation, submitted NDA 21-200 for the treatment of _____
in patients with irritable bowel syndrome (IBS) who identify _____
_____ constipation as their predominant symptoms”.

In a letter dated August 11, 2000, the Agency notified the sponsor that the new drug application was approvable. After reviewing the sponsor's response to the Approvable Letter, the Agency notified the sponsor in a letter dated June 15, 2001, that the application was not approvable.

On February 28, 2002, following discussions with the Agency, the sponsor submitted a complete response to the June 15, 2001 not approvable letter. This response contained additional safety data, a proposal for a risk management program, and revised labeling.

On June 19 and 26, 2002, the Agency met with the sponsor to discuss issues concerning the review of the application and proposed labeling for Zelnorm™.

On July 01, 2002, the sponsor submitted draft labeling in response to the Agency's comments in the June 26, 2002, meeting.

THE CALL:

The sponsor's draft labeling, submitted July 01, 2002, was used as reference for discussion in this meeting (see attachment).

The sponsor was informed that discussion about the patient package insert would occur at a later meeting after agreements have been reached on the package insert.

LABELING DISCUSSION

The sponsor was informed that the proposed revisions to the Prescribing Information insert were acceptable, except for the following changes.

Under the **CLINICAL STUDIES** (*Alternative 2*) section, the Agency recommended the addition of weeks 8 and 12 to the proposed chart.

[]

The sponsor was informed that depiction of the drug effect for the duration of the treatment period is a better description of the data because some patients showed

improvement during week 1 and some patients showed improvement during week 2, but the proposed weekly data does not indicate if the same patient had improvement over the course of treatment.

The sponsor agreed to the Agency's request to add weeks 8 and 12 to the chart.

Referencing lines 170-174, the sponsor was requested to provide data that supports the claim that

[The Agency informed the sponsor that in order to support the claim that the effect persisted throughout the treatment period, the data from patient analyses should show sustained individual effect over time vs. drug effect on groups over time.]

The sponsor indicated that it would amend the sentence to read

[The sponsor also agreed to submit analyses supporting the claim for bloating scores.]

The sponsor was requested to delete the sentence ' _____

The sponsor agreed to delete the lines.

Under the section, _____ **Induced Diarrhea**, the sponsor was requested to simplify the sentence "In most cases, the diarrhea occurred"]

The sponsor agreed to simplify the sentence and to submit the revised wording to the Agency for review.

Under the **DOSAGE AND ADMINISTRATION** section, the sponsor was asked how soon after taking Zelnorm was the patient given a meal during clinical trials.

The sponsor stated that patients received a meal within 30 minutes after taking Zelnorm.

The sponsor was requested to delete ' _____

The sponsor was requested to revise the statement:

From: "The recommended dosage of ZELNORM™ (tegaserod maleate) is 6 mg _____ orally _____

To: “The recommended dosage of ZELNORM™ (tegaserod maleate) is 6mg before meals for 4 to 6 weeks.”

The sponsor agreed to the change.

CONCLUSION

1. The sponsor will submit revised labeling to the Agency for review.

**APPEARS THIS WAY
ON ORIGINAL**